

Pancreatic cancer

TRACO-2019

Pancreatic Cancer: From Bench to Bedside



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Incidence and mortality

Pancreatic Cancer Incidence and Mortality

Estimated Deaths

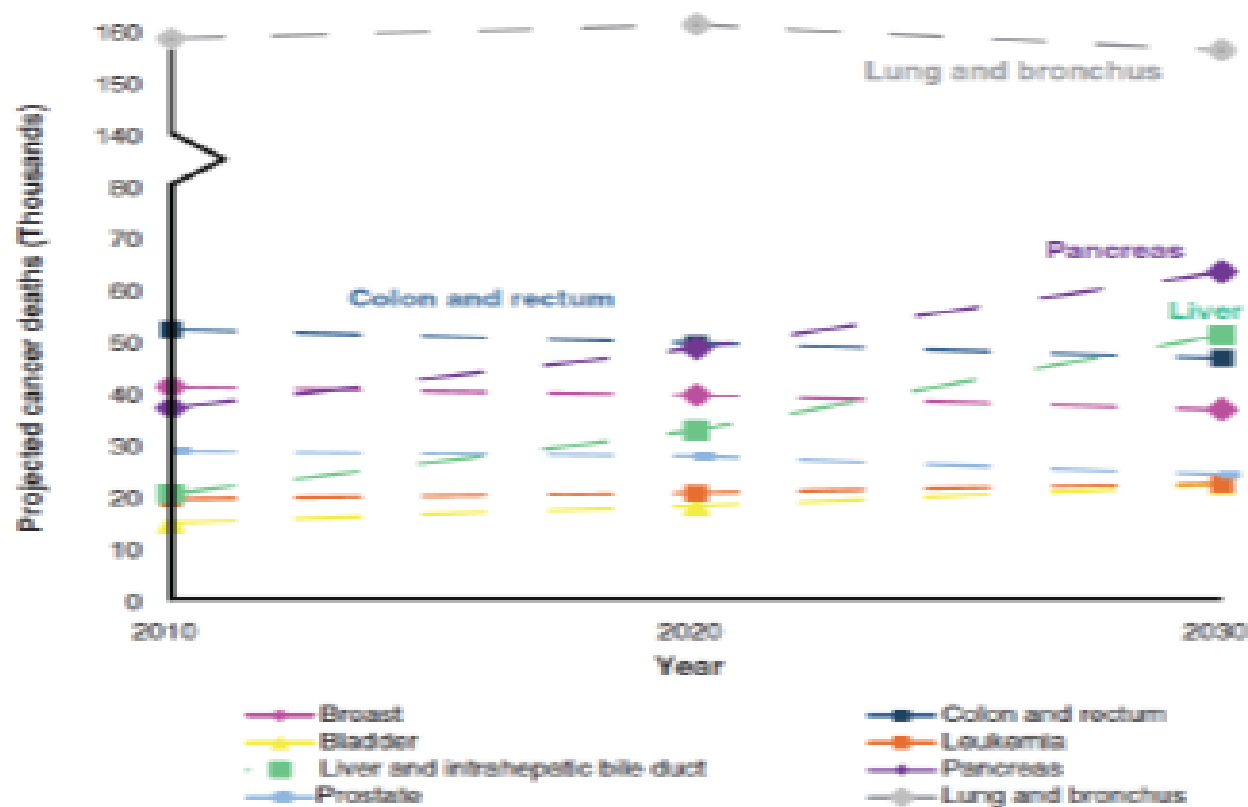
Siegel R et. al., CA Cancer J Clin, 2018

			Males	Females			
Lung & bronchus	83,550	26%			Lung & bronchus	70,500	25%
Prostate	29,430	9%			Breast	40,820	14%
Colon & rectum	27,390	8%			Colon & rectum	23,240	8%
Pancreas	23,020	7%			Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%			Ovary	14,070	5%
Leukemia	14,270	4%			Uterine corpus	11,350	4%
Esophagus	12,850	4%			Leukemia	10,100	4%
Urinary bladder	12,520	4%			Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%			Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%			Brain & other nervous system	7,340	3%
All Sites	323,630	100%			All Sites	286,010	100%

- 3rd leading cause of cancer death in the United States
- Median 5 year survival is 9%
- Median overall survival is < 6 months
- Estimated 55,440 new diagnoses and 44,330 deaths in 2018

Deaths annually increasing

Pancreatic Cancer: Second Leading Cause of Cancer-related Deaths by 2030



Risk factors

Risk Factors

Ryan, Hong and Bardeesy, NEJM, 371, 2014

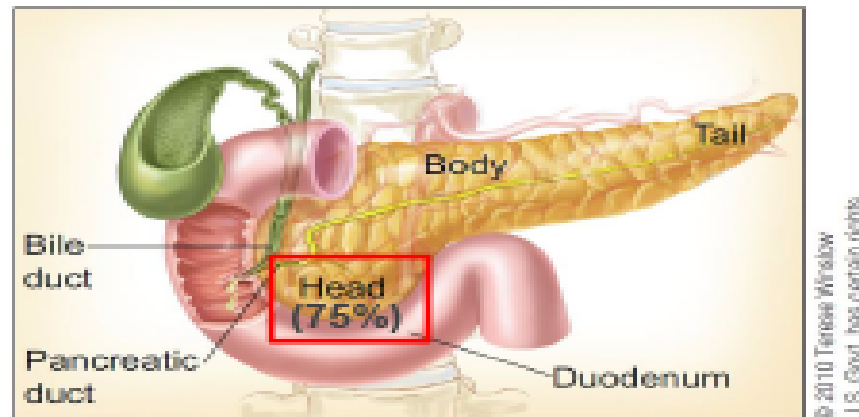
Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.*

Variable	Approximate Risk
Risk factor	
Smoking ³	2–3
Long-standing diabetes mellitus ⁴	2
Nonhereditary and chronic pancreatitis ⁵	2–6
Obesity, inactivity, or both ⁶	2
Non-O blood group ⁷	1–2
Genetic syndrome and associated gene or genes — %	
Hereditary pancreatitis (<i>PRSS1</i> , <i>SPINK1</i>) ⁸	50
Familial atypical multiple mole and melanoma syndrome (<i>p16</i>) ⁹	10–20
Hereditary breast and ovarian cancer syndromes (<i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i>) ^{10,11}	1–2
Peutz-Jeghers syndrome (<i>STK11</i> [<i>LKB1</i>]) ¹²	30–40
Hereditary nonpolyposis colon cancer (Lynch syndrome) (<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i>) ¹³	4
Ataxia-telangiectasia (<i>ATM</i>) ¹⁴	Unknown
Li-Fraumeni syndrome (<i>P53</i>) ¹⁵	Unknown

* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.

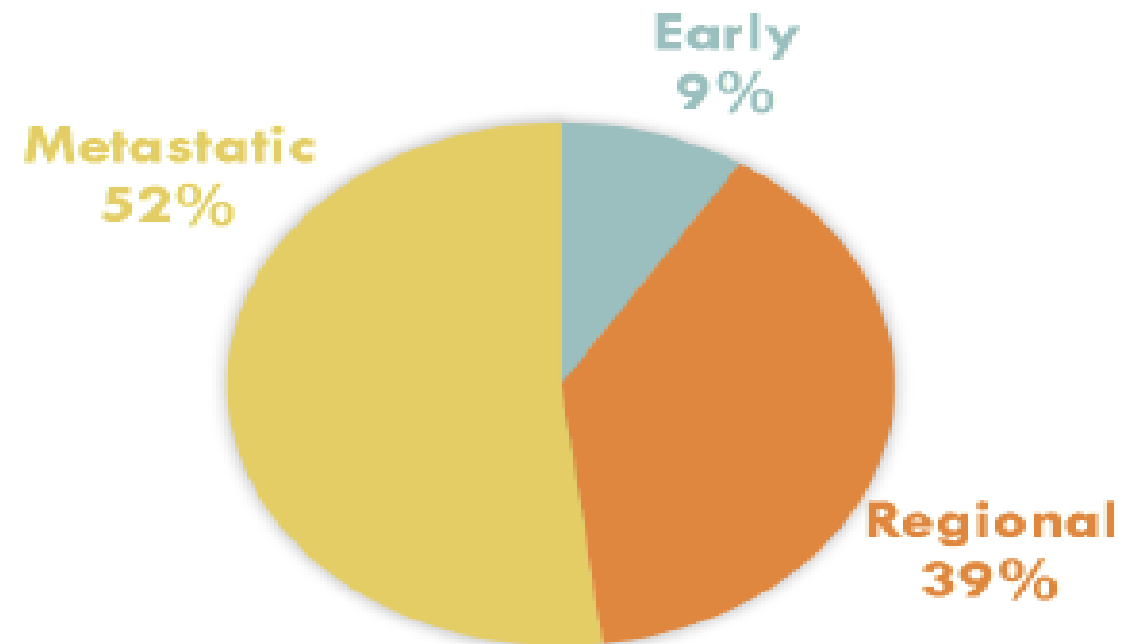
Types and stage

Pancreatic Cancer: Types and Stage at Diagnosis



- **Adenocarcinoma (~90%)**
- Neuroendocrine (<5%)
- Adenosquamous
- Acinar Cell Carcinoma
- Mucinous cystadenocarcinoma

American Cancer Society, *Cancer Facts and Figures 2017*



Early detection

Why can't we detect pancreatic cancer earlier?

- ❖ Early symptoms are non-specific
- ❖ Current imaging methods rarely detect small lesions
- ❖ Difficulty in identifying specific biomarkers
 - ❖ Pancreatic Cancer is relatively rare (12.1/ 100,000 persons)
 - ❖ Test with 100% sensitivity and 99% specificity => 83 false positive for every real case
- ❖ Retroperitoneal positioning of the pancreas makes biopsy difficult
- ❖ Risk vs. benefit of removing suspicious pre-cursor lesions

Carbohydrate antigen 19-9

Carbohydrate Antigen 19-9 (CA19-9)

Serum CA19-9 >37 U/ml

Pancreatic Cancer vs Healthy Individual

Sensitivity: 80.3% (95% CI 77.2-82.6)

Specificity: 80.2% (95% CI 78-82.3)

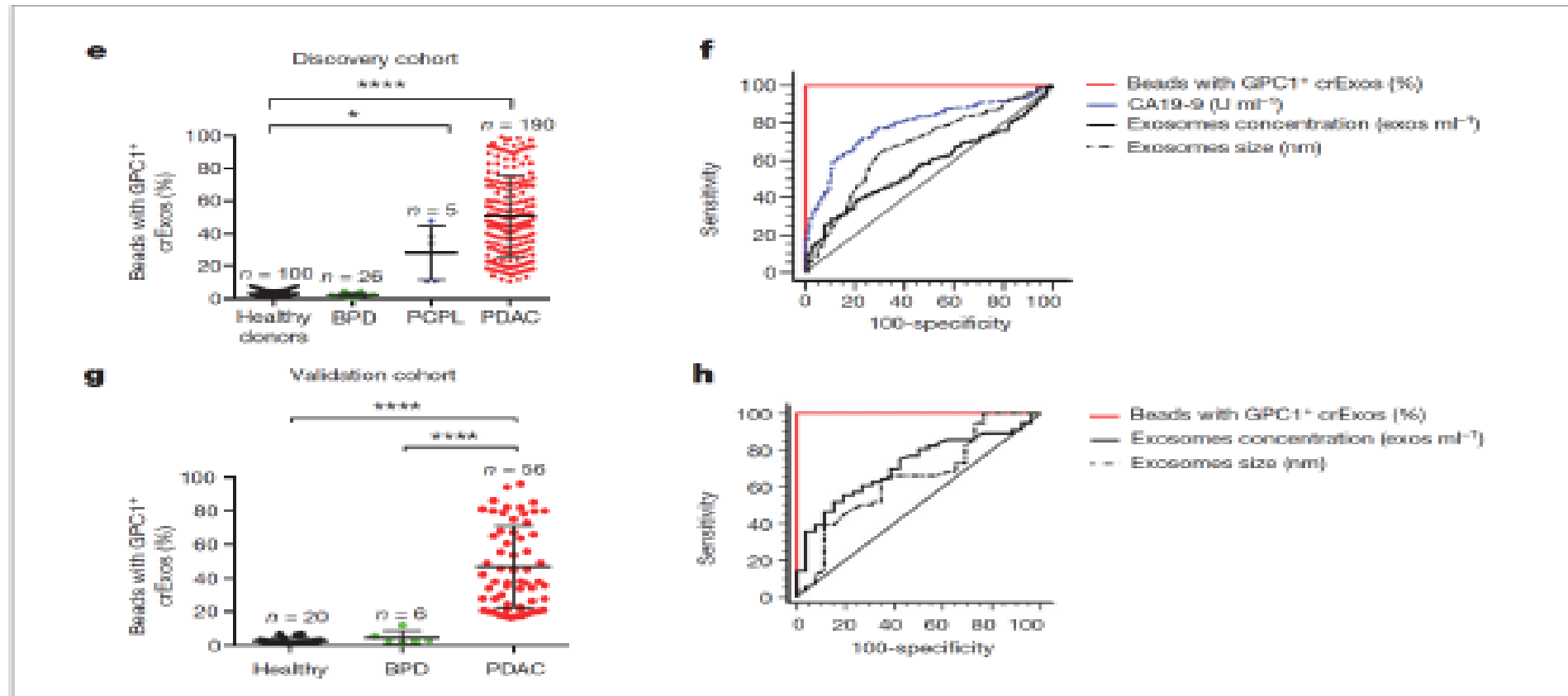
Malignant vs Benign Pancreatic Disease

Sensitivity: 78.2%

Specificity: 82.2%

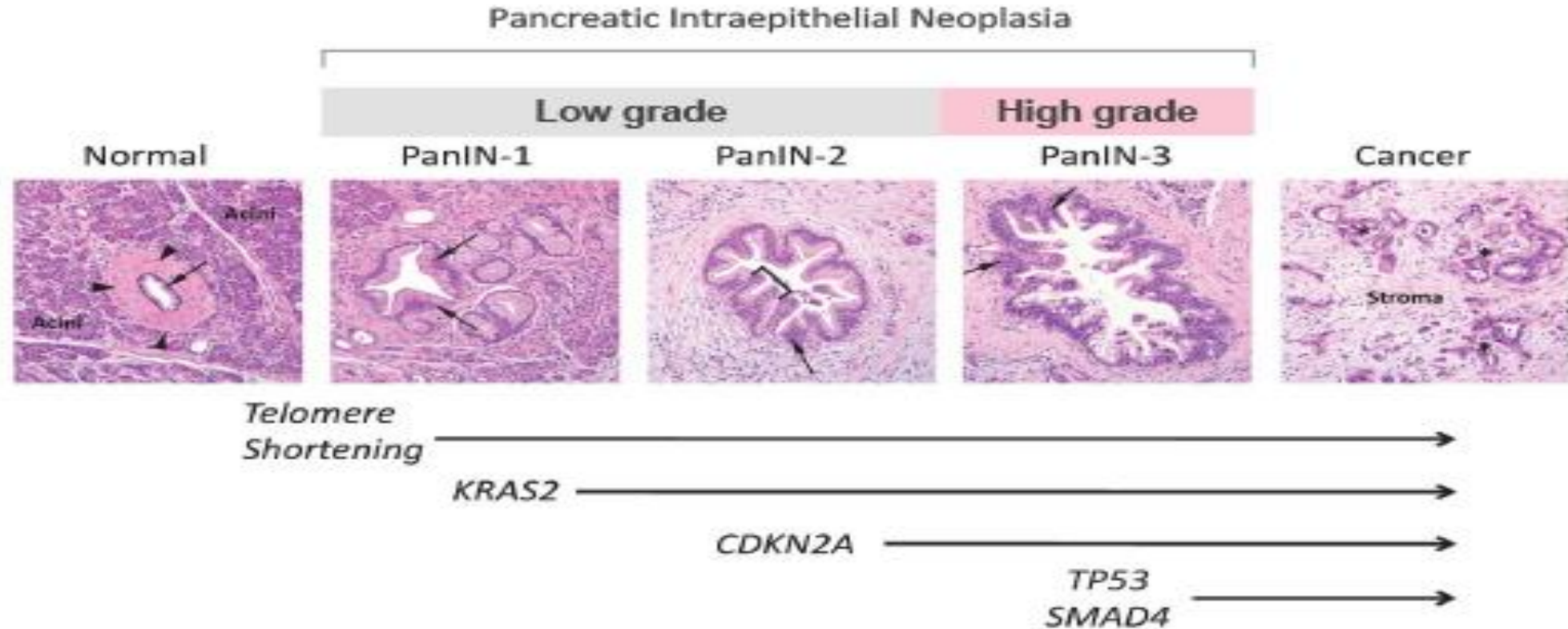
Glypican-1 positive exosomes

Glypican-1 Positive Circulating Exosomes as a Biomarker for PDAC



Carcinogenesis

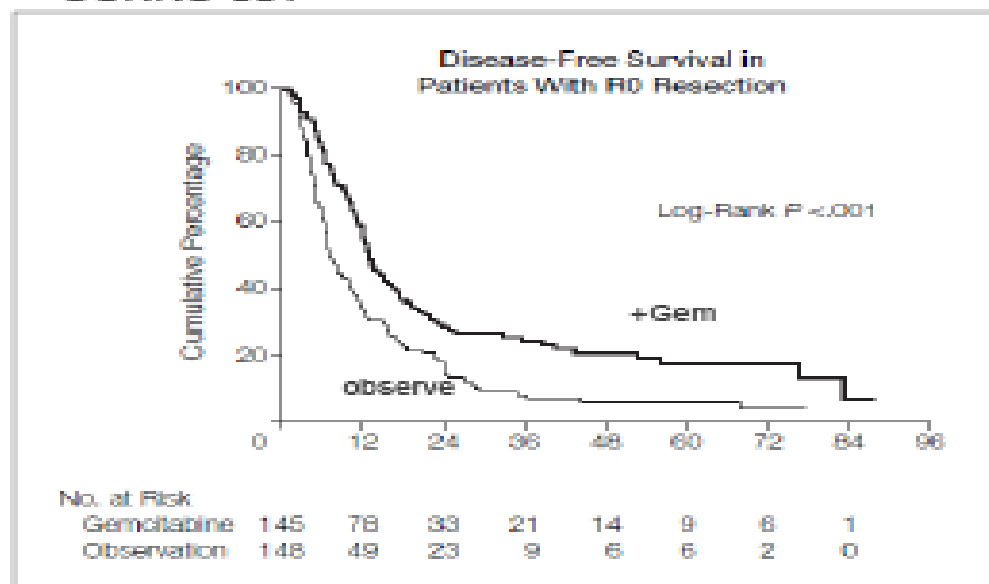
Progression Model of Pancreatic Carcinogenesis



Early stage disease

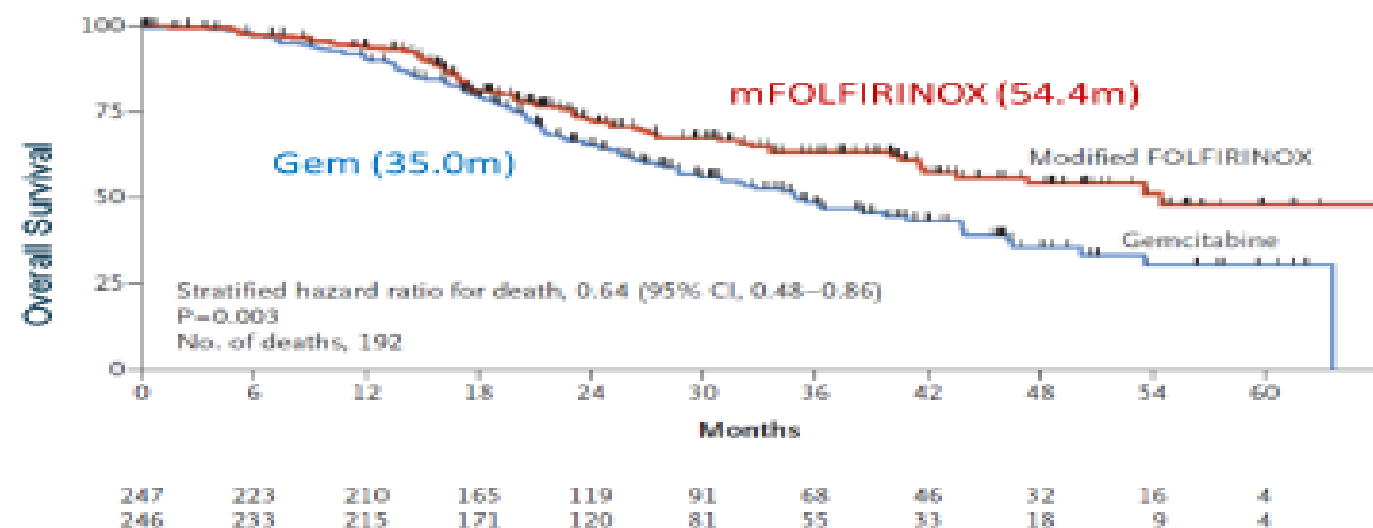
Early Stage Disease: Surgery + Chemotherapy

CONKO-001



Oettle et al, *JAMA*, 2007

PRODIGE/ ACCORD



Conroy et al, *NEJM*, 2018

Neoantigen qualities

LETTER

doi:10.1038/nature24462

Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer

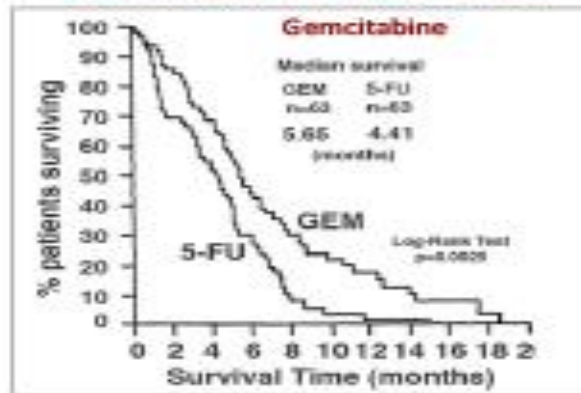
Vinod P. Balachandran^{1,2,3}, Marta Luksza⁴, Julia N. Zhao^{1,3,5}, Vladimir Makarov^{5,6}, John Alec Moral^{1,2,3}, Romain Remark⁷, Brian Herbst², Gokce Askan^{2,8}, Umesh Bhanot⁸, Yasin Senbabaoglu⁹, Daniel K. Wells¹⁰, Charles Ian Ormsby Cary¹⁰, Olivera Grbovic-Huezo², Marc Attiyeh^{1,2}, Benjamin Medina¹, Jennifer Zhang¹, Jennifer Loo¹, Joseph Saglimbeni², Mohsen Abu-Akeel⁹, Roberta Zappasodi⁹, Nadeem Riaz^{6,11}, Martin Smoragiewicz¹², Z. Larkin Kelley^{13,14}, Olca Basturk⁸, Australian Pancreatic Cancer Genome Initiative⁺, Mithat Gönen¹⁵, Arnold J. Levine⁴, Peter J. Allen^{1,2}, Douglas T. Fearon^{13,14}, Miriam Merad⁷, Sacha Gnajatic⁷, Christine A. Iacobuzio-Donahue^{2,5,8}, Jedd D. Wolchok^{3,9,16,17,18}, Ronald P. DeMatteo^{1,2}, Timothy A. Chan^{3,5,6,11}, Benjamin D. Greenbaum¹⁹, Taha Merghoub^{3,9,18} & Steven D. Leach^{1,2,5,20}

- Highest neoantigen number
- Abundant CD8⁺ T Cell Infiltrate
- Neoantigen quality promotes T Cell Activity in Long-term survivor

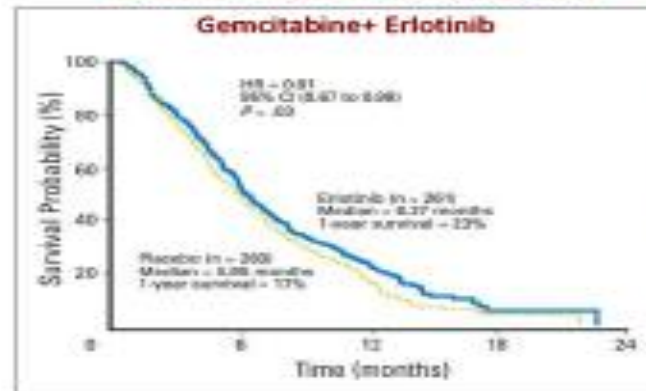
Cancer treatment

Disappointing Progress in the Treatment of Pancreatic Cancer

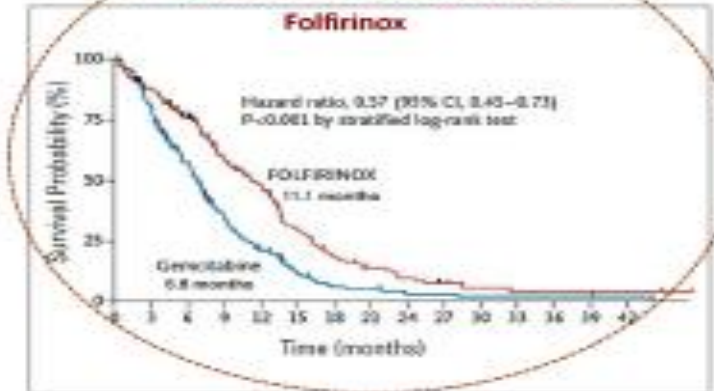
Burris et. al., J. Clin. Oncol., 15, 1997



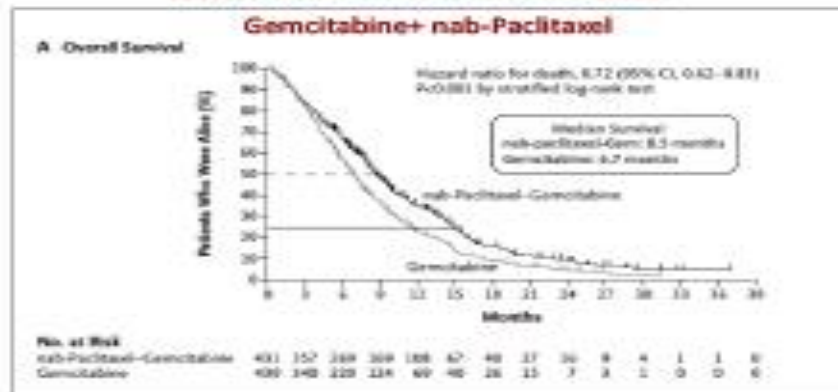
Moore et. al., J. Clin. Oncol. 25, 2007



Conroy et. al., NEJM, 36, 2011



Von Hoff, D.D. et. al, NEJM, 369, 2013

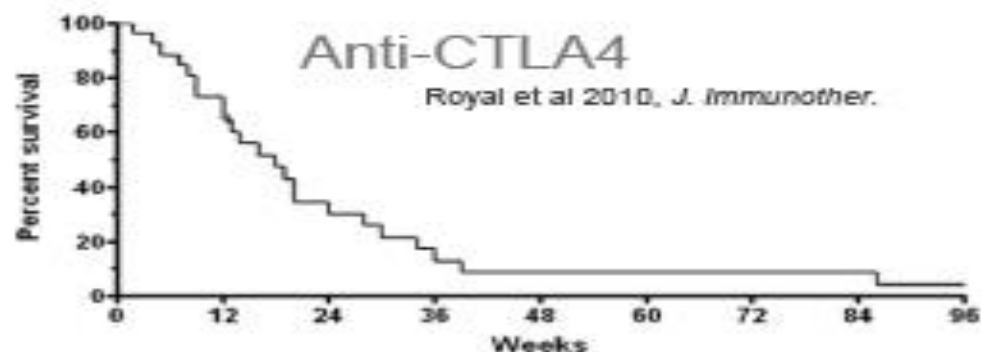


Wang-Gillam A., et. al., Lancet, 2015



Immune checkpoint blockade

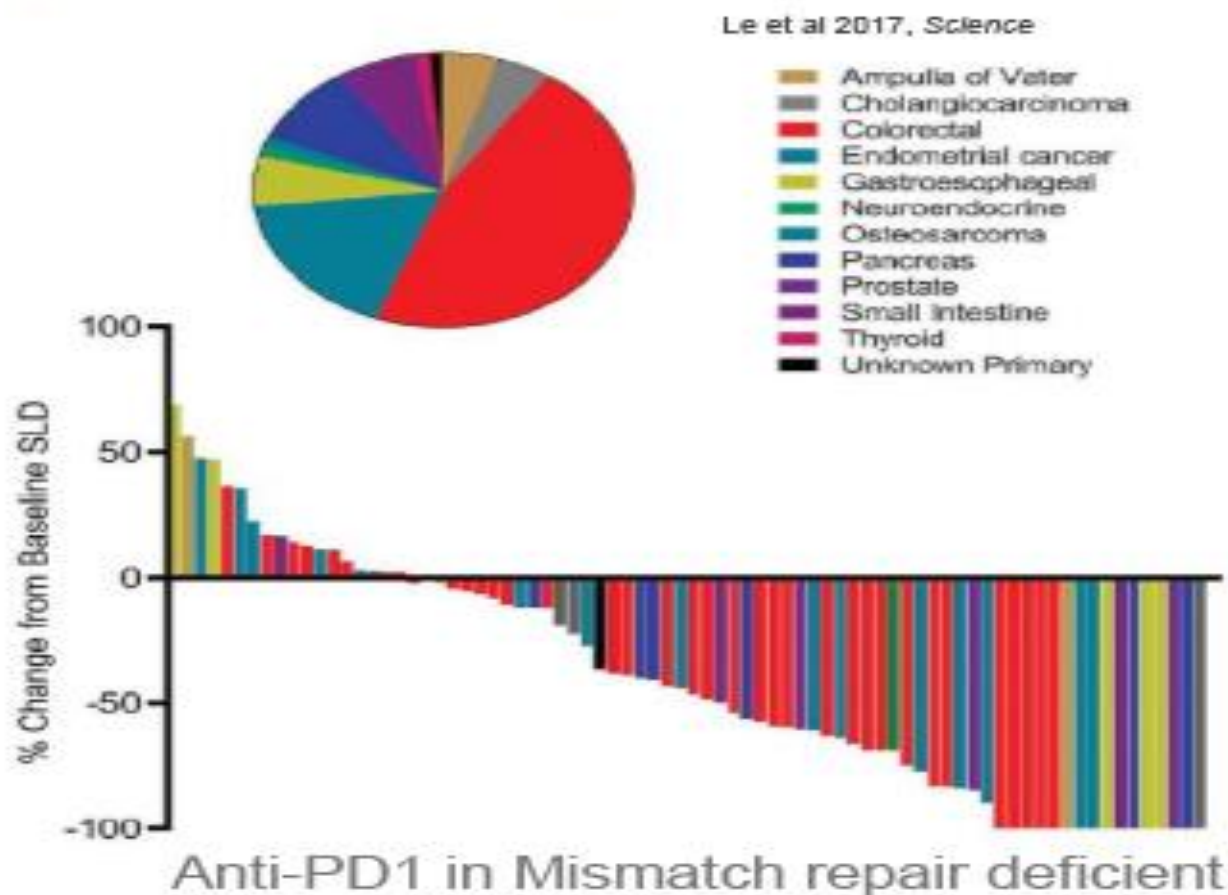
The disappointment of immune checkpoint blockade in pancreatic cancer



Anti-PD1

Cohort-Tumor Type	N*	ORR %	mPFS (mo)	mOS (mo)
Overall	471	14	2.2	11.3
Mesothelioma (MPM)	25	20	5.5	18.7
Nasopharyngeal Carcinoma	27	26	6.5	16.6
Neuroendocrine Carcinomas	16	6	4.5	21
Ovarian Epithelial FTC/PPC	26	12	1.9	13.8
Pancreatic ACA	24	0	1.7	3.9
Prostate ACA	23	17	3.5	7.9
Salivary Gland Carcinoma	26	12	3.8	13.2
SCLC	24	33	1.9	9.7

Ott et al 2019, *J. Clin. Onc.*



Novel immune therapies

Novel immunotherapies- an active area of investigation

- Make “cold” tumor hot by combining with agents that stimulate immune response
 - Radiation
 - Tumor vaccine
 - Oncolytic virus
 - Chemotherapy
- CSF-1R inhibitor: block cytokine signaling to relocate immunosuppressive macrophages
- CD40 agonist: reprogram poorly functioning ADC's
- Block other checkpoints

Genetic alterations

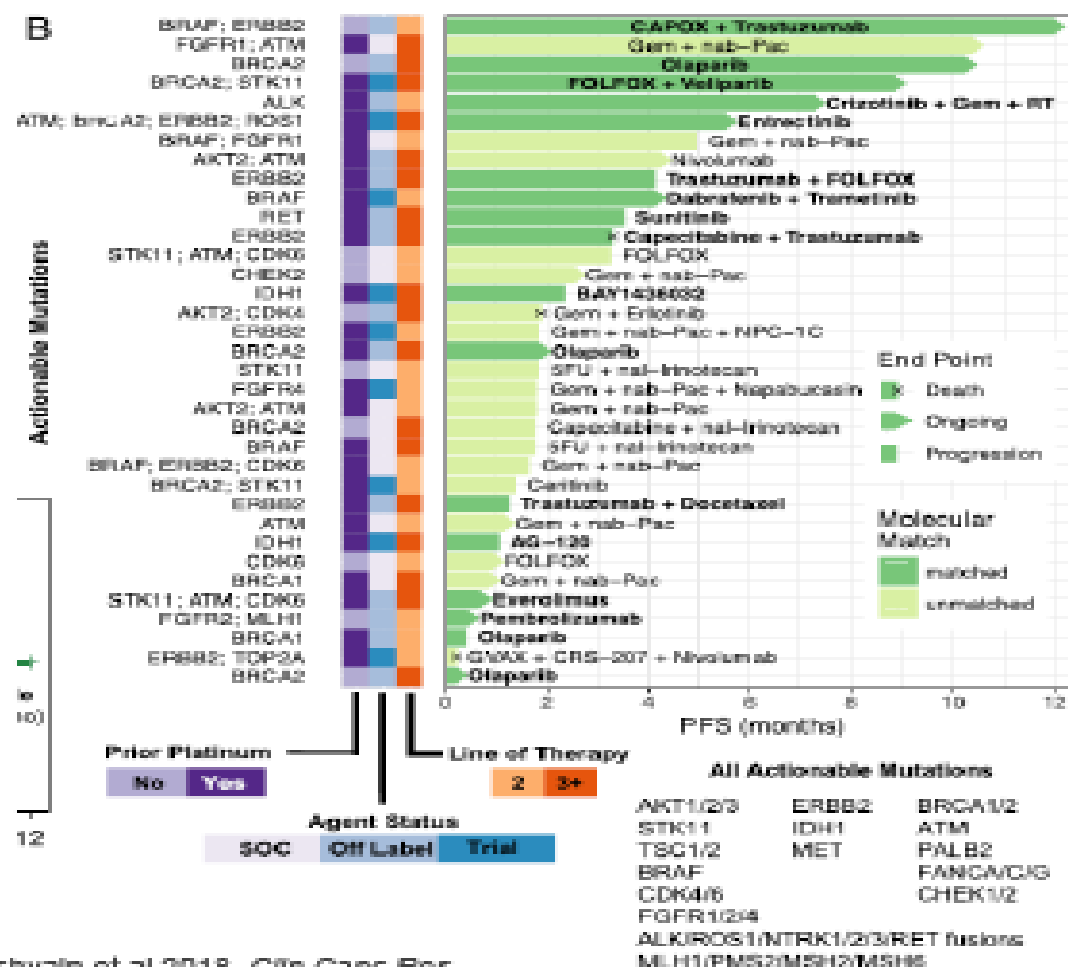
Gene Alterations in Pancreatic Cancer



Precision medicine

Know Your Tumor: Precision Medicine for PDAC

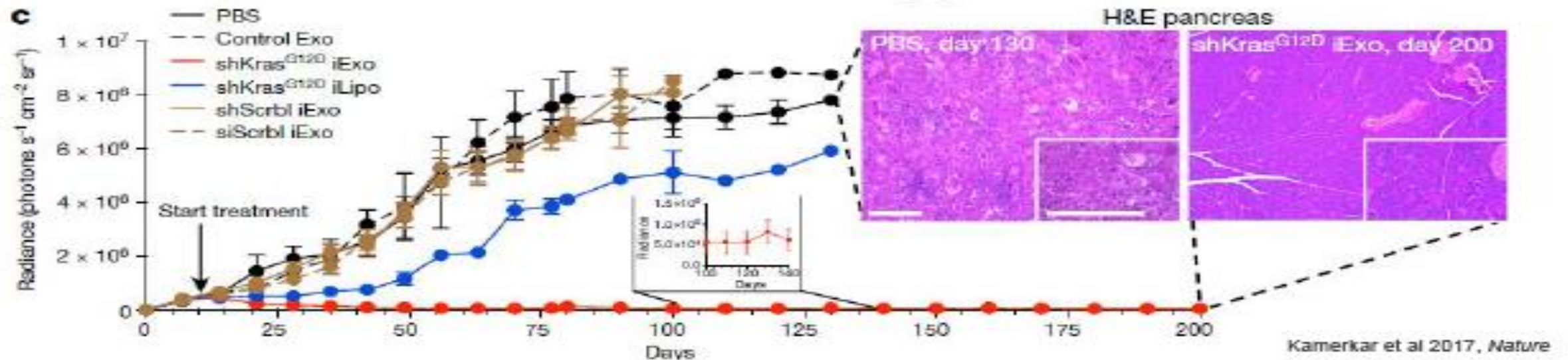
- N = 640 patients accrued
- Adequate samples for sequencing in >90%
- “50% with actionable mutations (27% highly actionable)”
 - DNA repair genes (BRCA, ~8%)
 - Cell cycle genes (CCND1/2/3, CDK4/6, ~8%)
- Effect of matched therapy
 - N = 18
 - PFS 4.1 vs. 1.9 m (HR 0.47, p = 0.03)



iExosomes

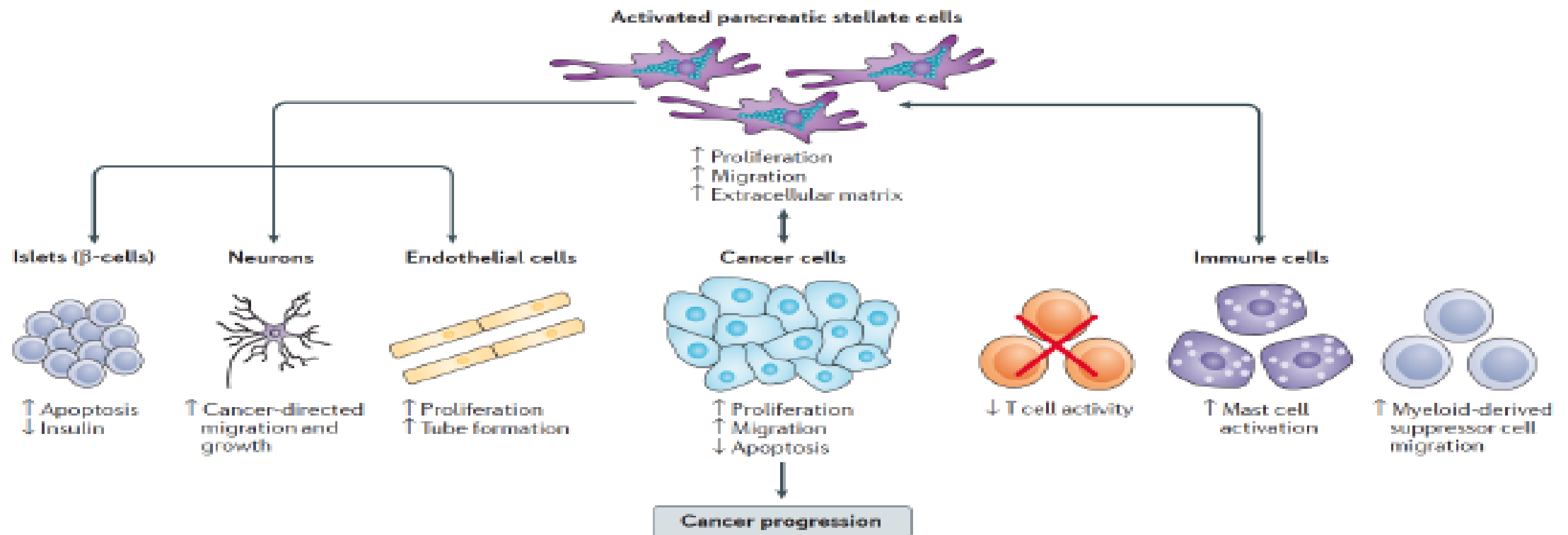
iExosomes for delivery of siRNA targeting mutant KRAS

- Package anti-KRAS^{G12D} siRNA into artificial iExosomes
 - Exosomes are more resistant to ingestion by macrophages in circulation than liposomes
 - iExosomes preferentially accumulate in liver, pancreas and lungs
- Increased macropinocytosis in KRAS mutant cells => increased uptake of iExosomes
- No toxicity seen; no effect on KRAS WT cells



Complex microenvironment

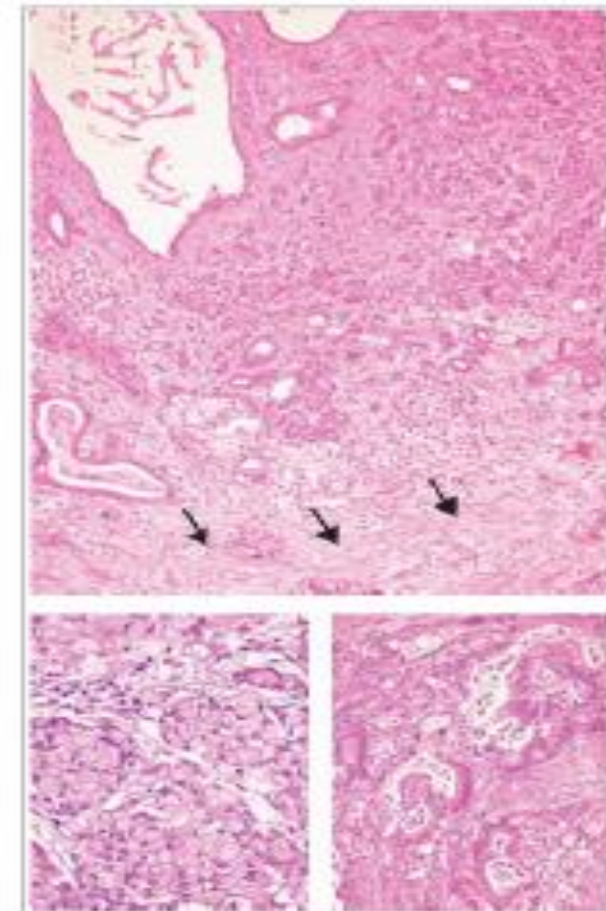
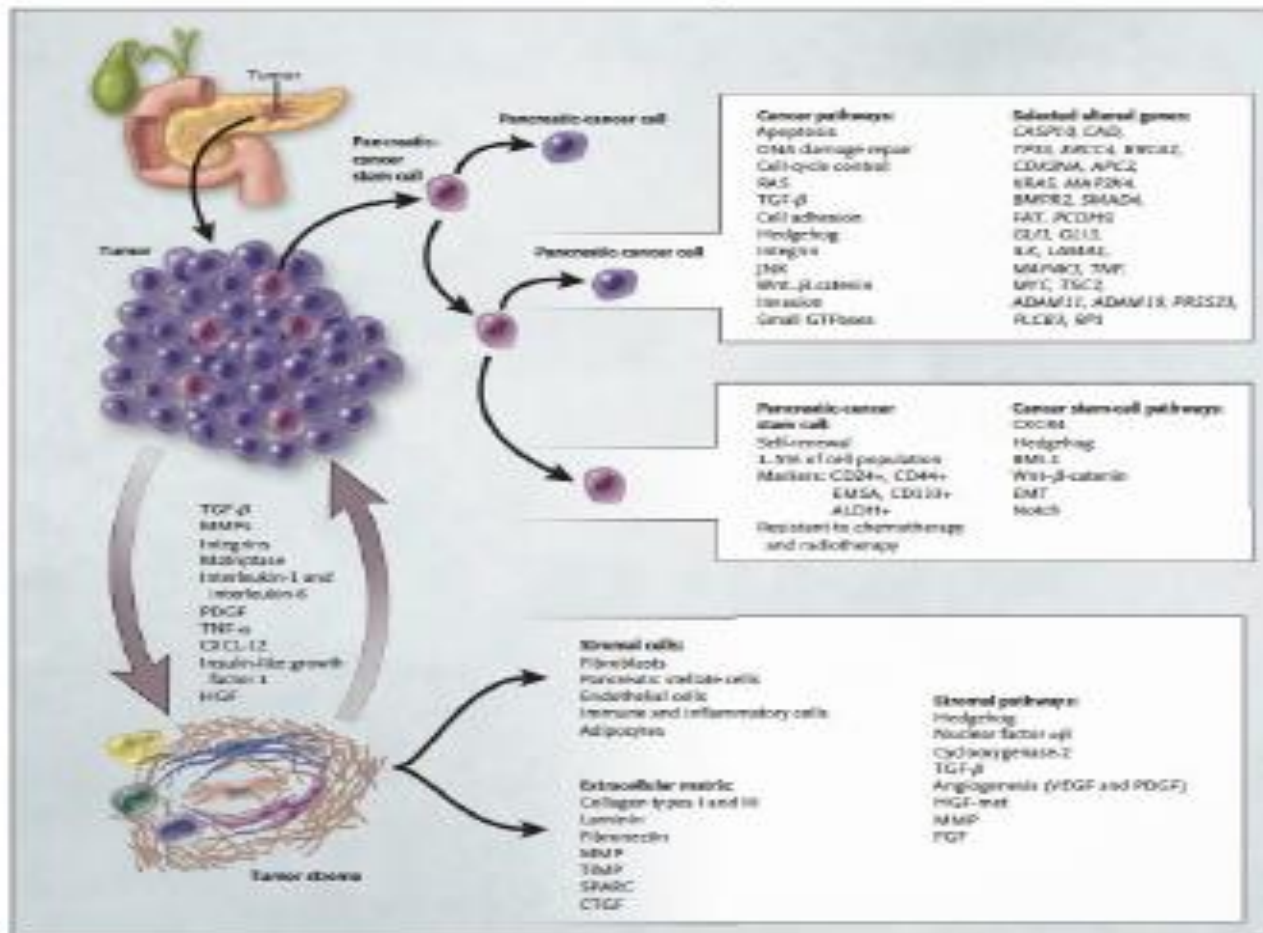
The complex microenvironment of pancreatic cancer



Kleeff, J. et al. (2016) Pancreatic cancer
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.22

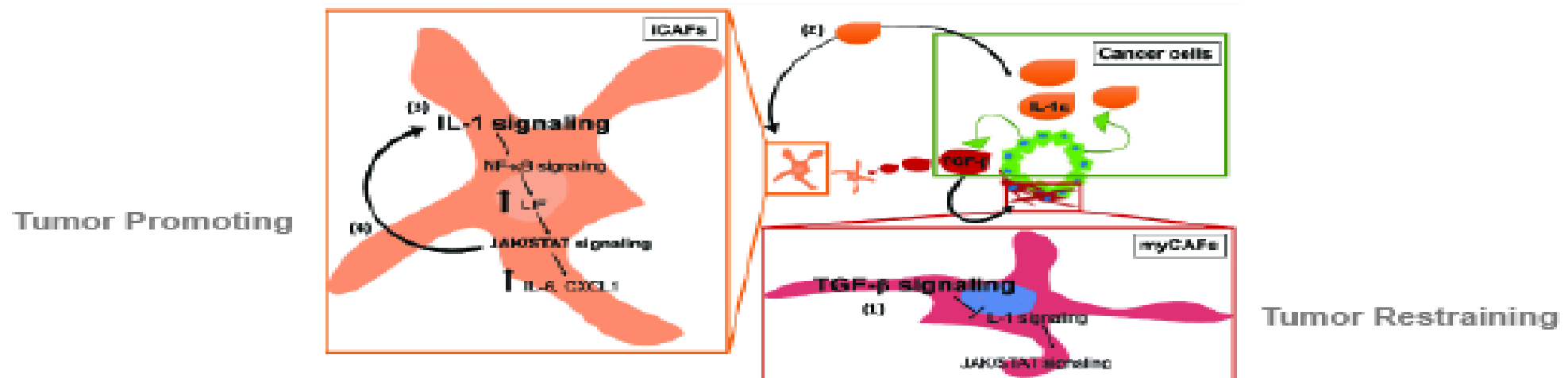
Desmoplastic stroma

Prominent Desmoplastic Stroma in Pancreatic Cancer



Cancer associated fibroblasts

Cancer associated fibroblast (CAF) heterogeneity and stromal targeting in PDAC



Tumor secreted Ligands TGF- β and IL-1 promotes CAF heterogeneity

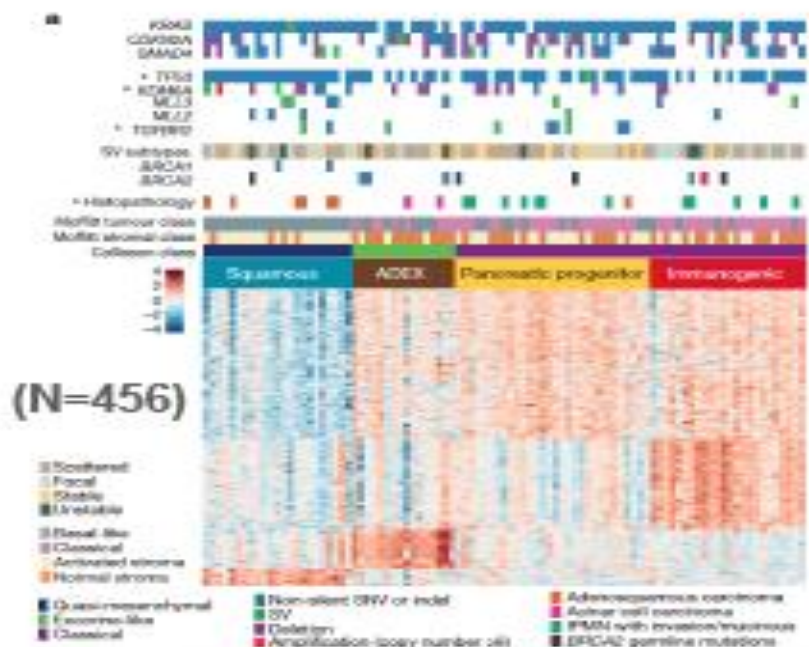
Targeting distinct Fibroblast niche- Tumor Promoting Inflammatory CAF

Tumor heterogeneity

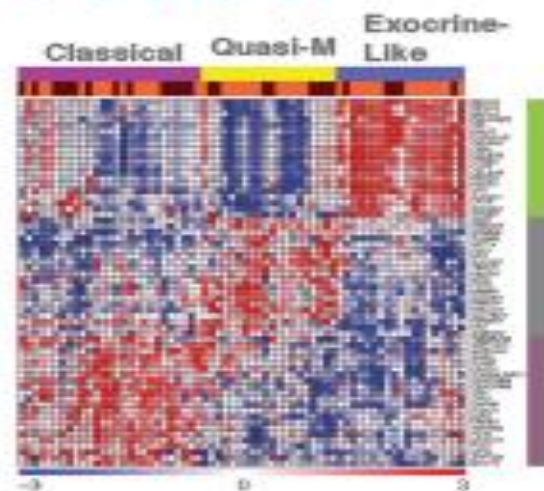
Tumor Heterogeneity and Molecular Subtypes

PDAC subtypes

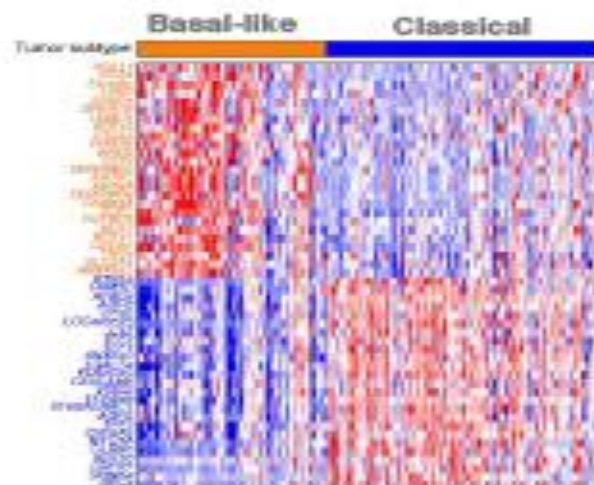
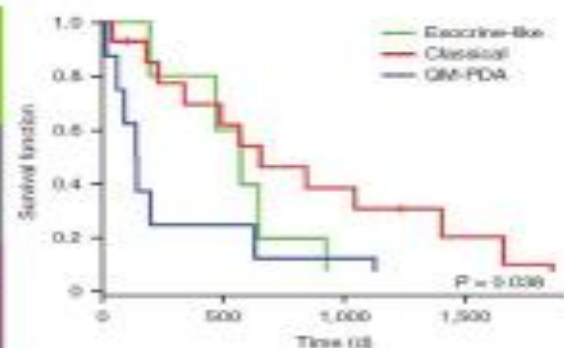
How many subtypes of PDAC are there?



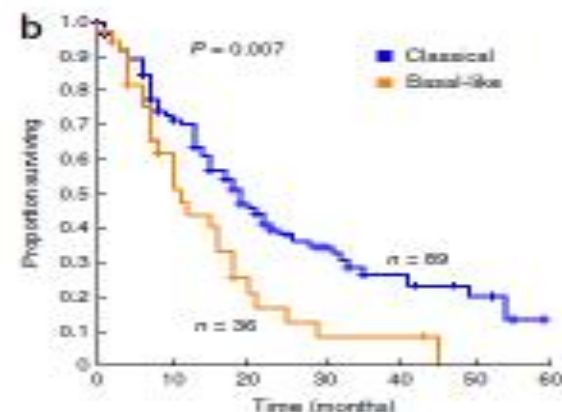
Bailey et. al., Nature, 2016



Collisson et. al., Nat. Med., 2011

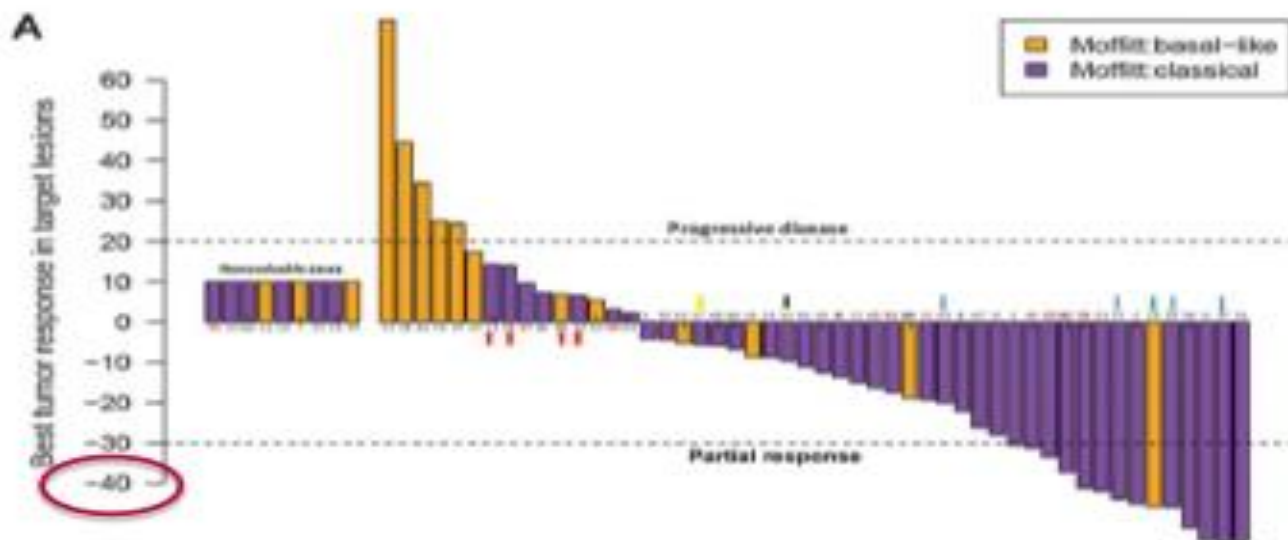


Moffitt et. al., Nat. Gen., 2015



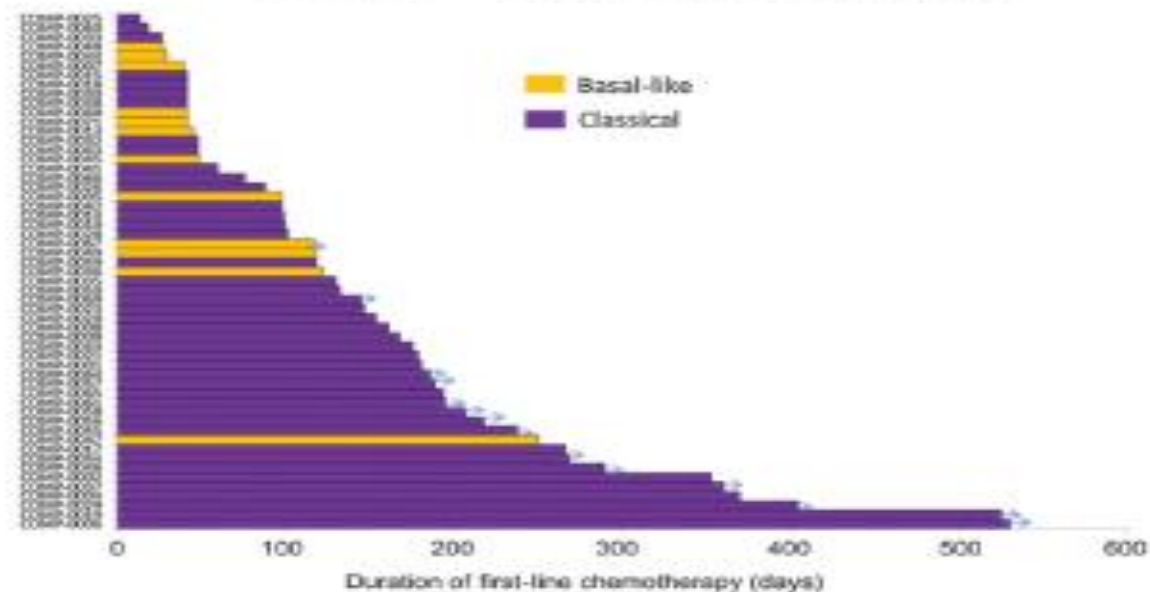
Classical subtype

Classical subtype responds better to chemotherapy



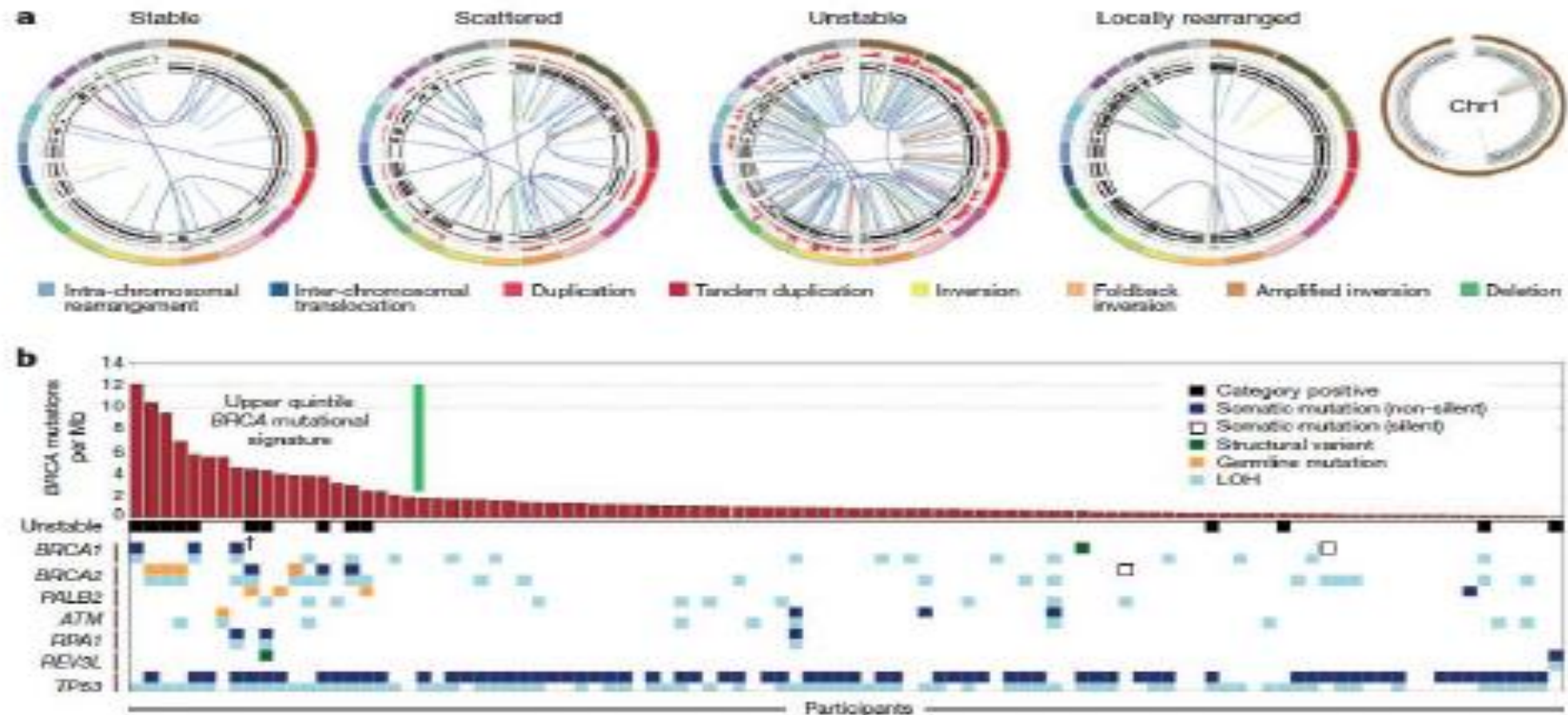
Waterfall plot: how deep is the response?
"Deep" = the tx shrinks the tumor a lot

Swimmer plot: how durable?
"durable" = the tx works a long time



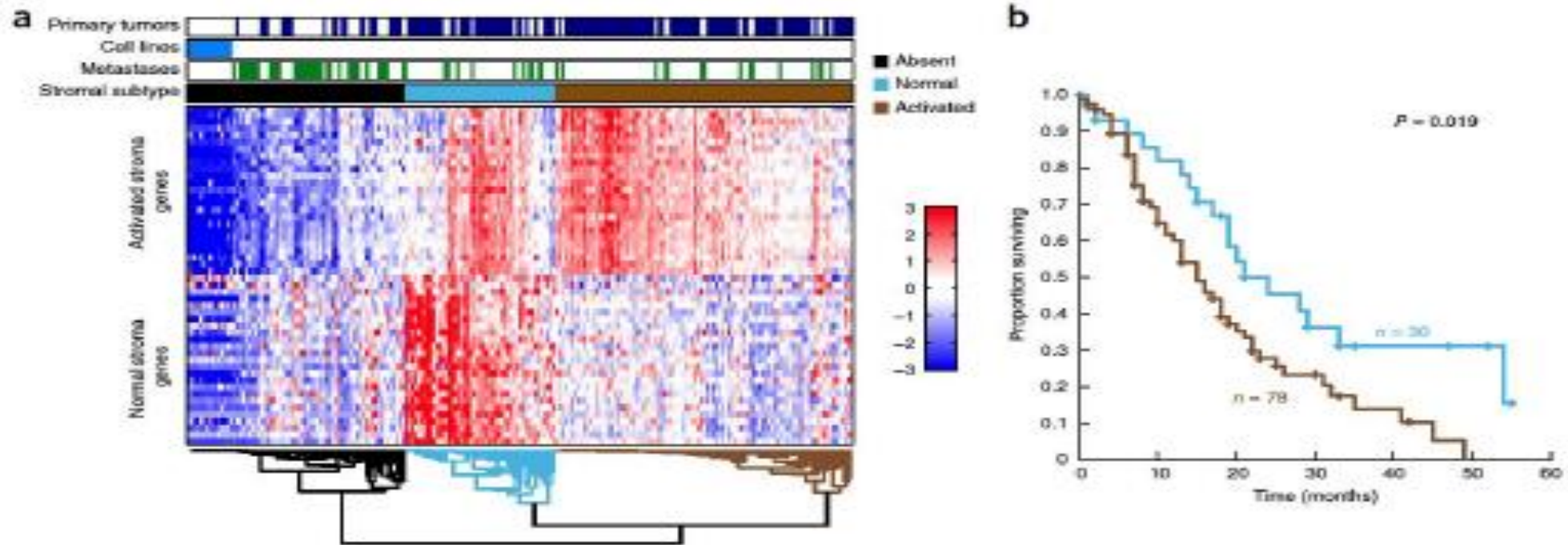
Chromosome structure

Variations in Chromosomal Structure and PDAC Subtypes



Stroma specific subtypes

Stroma-Specific Subtypes in Pancreatic Cancer

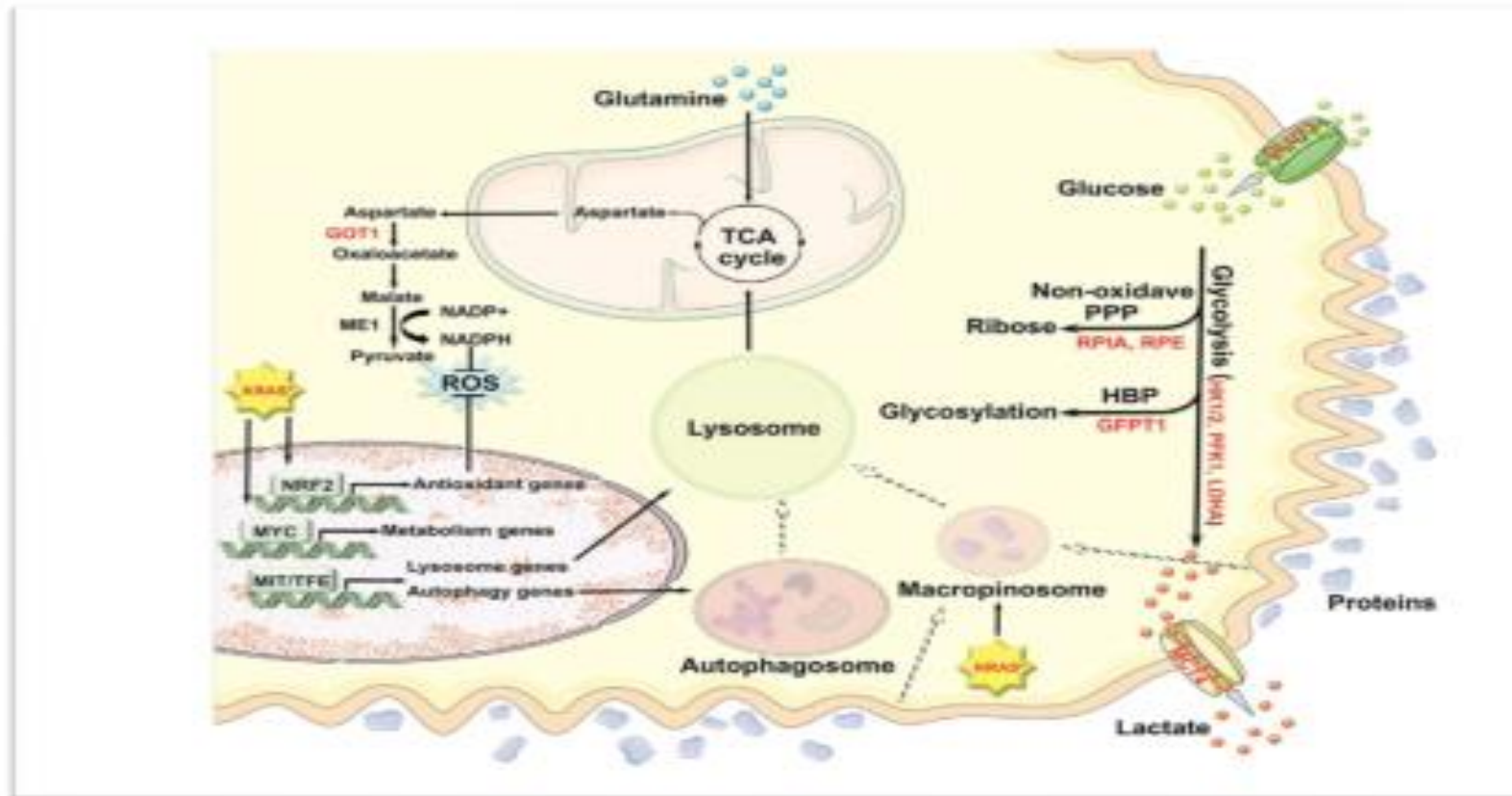


Moffitt et. al., Nature Genetics, 2015

Metabolic reprogramming

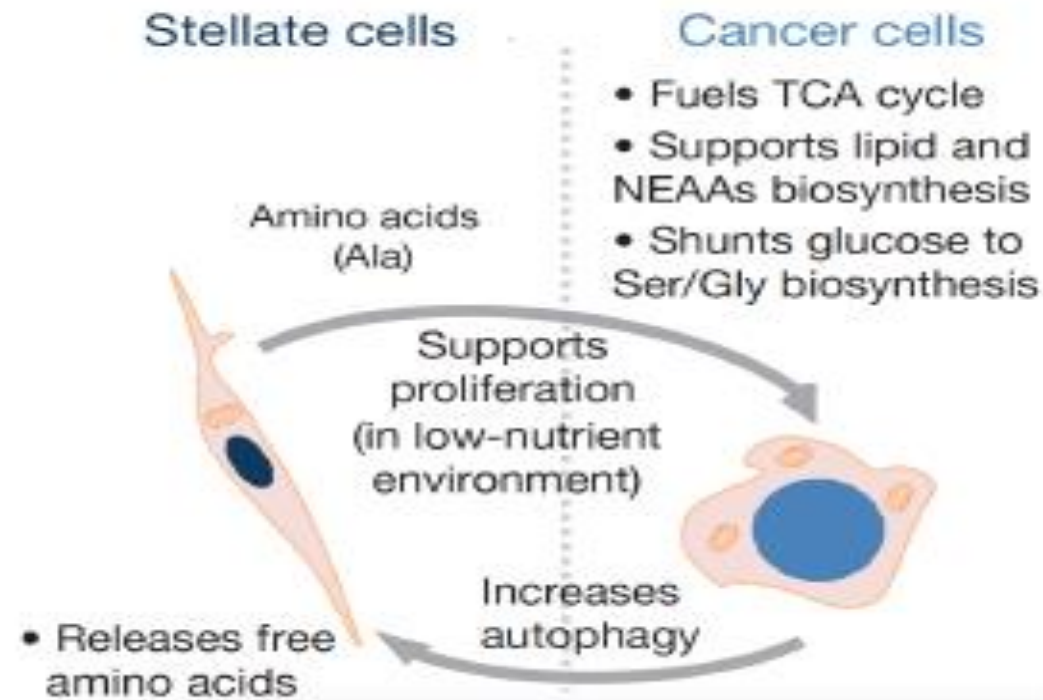
Metabolic Reprogramming in Pancreatic Cancer

Is this a treatment target?



Stellate cells

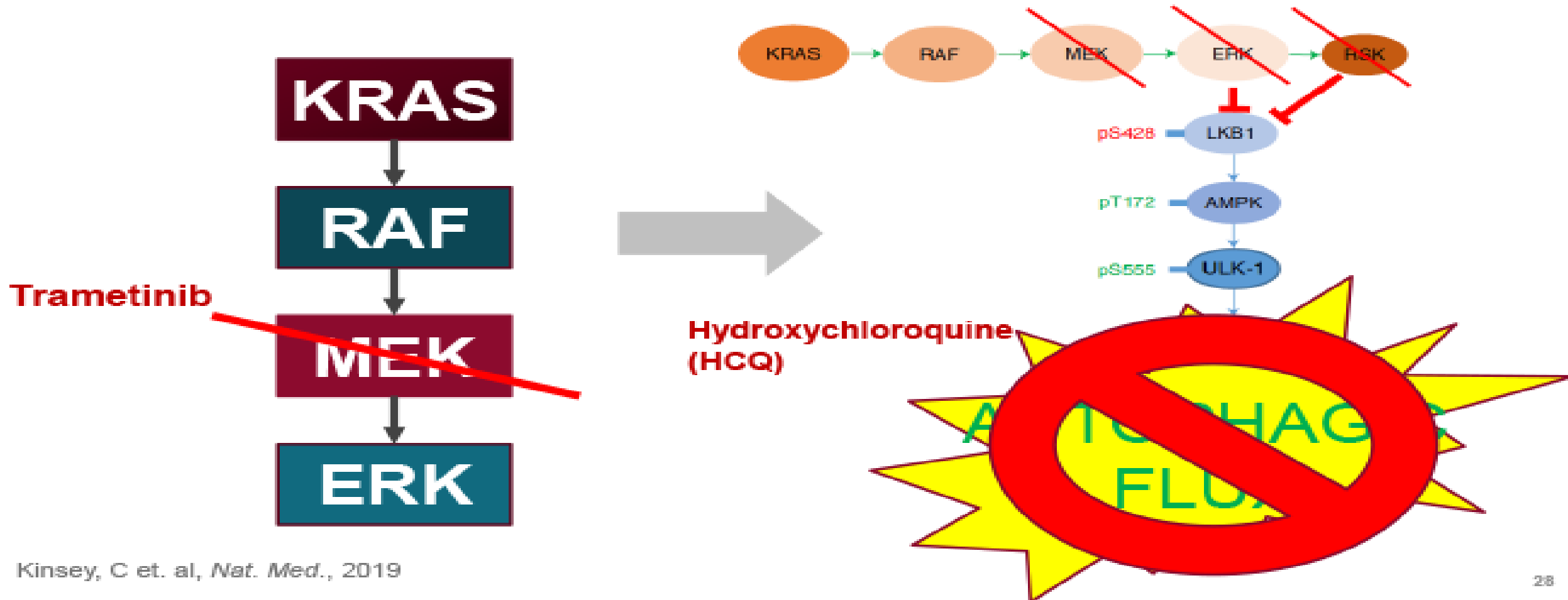
Pancreatic stellate cells support tumor metabolism



Sousa, et. al., Nature, 2016

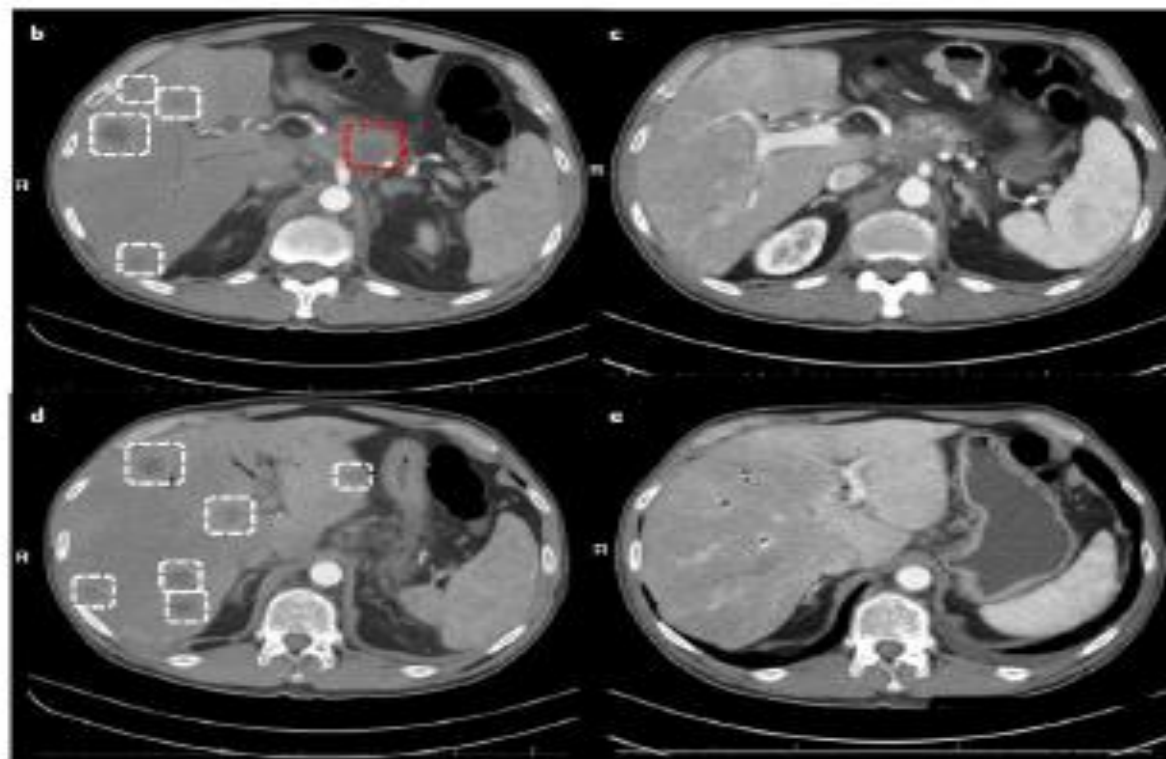
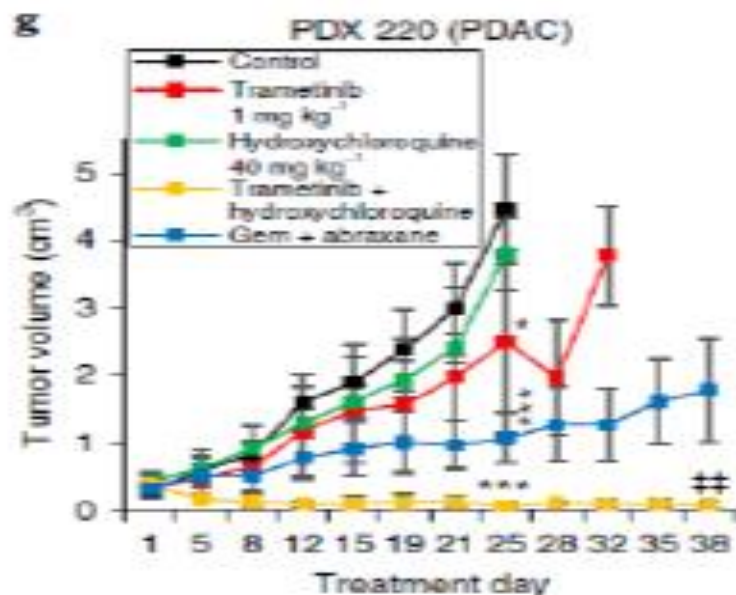
RAS/MAPK

Co-targeting of RAS/MAPK pathway and autophagy



Trametinib plus HCQ

Trametinib (MEK inhibitor) + HCQ (autophagy inhibition)



Drug delivery

Treatment Strategies to Improve Disease Outcome

*Drug Delivery
and
Effectiveness of Systemic Therapy*



Targeting Stroma

Mouse model

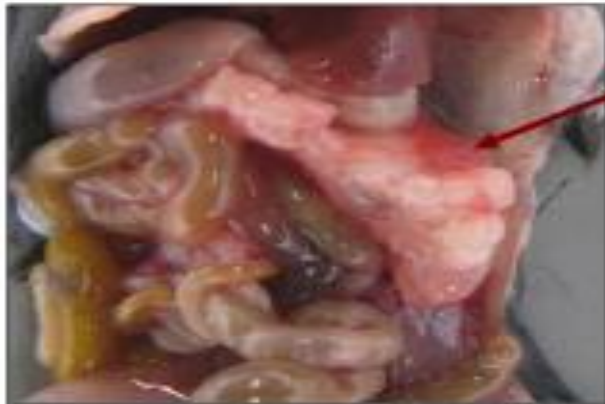
Pancreatic Cancer Mouse Model (KPC)

*LSL-Kras-G12D X p53 LSL R172H X Pdx-Cre 1

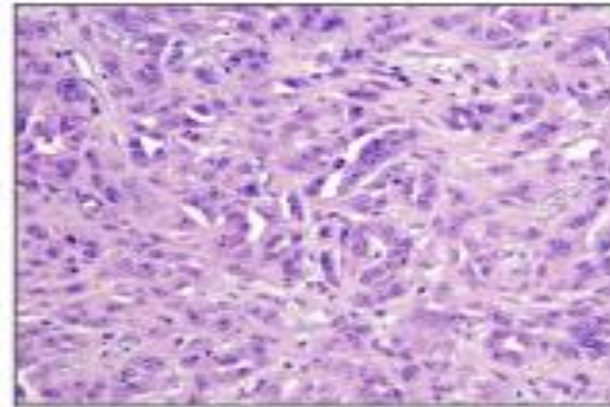


Pancreatic Ductal Adenocarcinoma (PDAC)

(Median Survival = 4-5 months)



PDAC

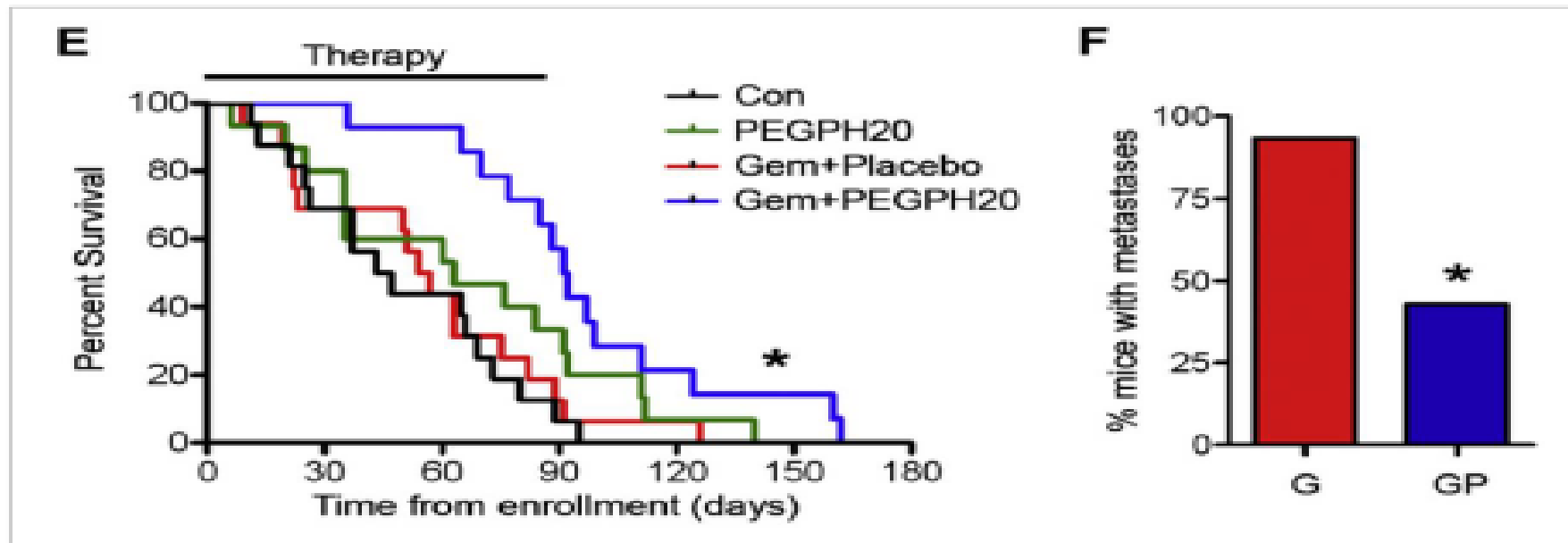


H&E

*Hingorani, S. et. al., Cancer Cell, 2005

Stroma targeting

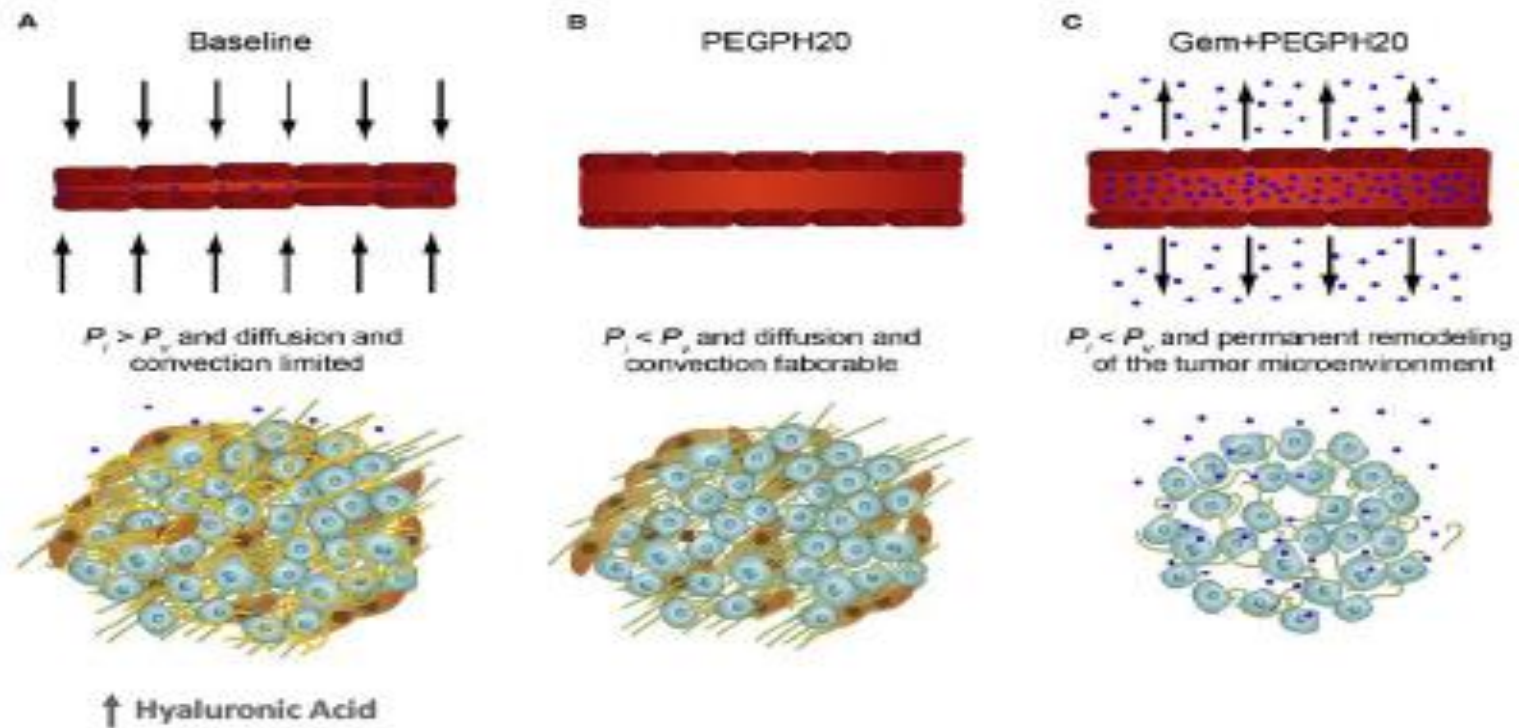
Enzymatic Targeting of Stroma Enhances Therapeutic Response



Provenzano et. al., Cancer Cell, 21, 2012

Therapeutic response

Enzymatic Targeting of Stroma Enhances Therapeutic Response



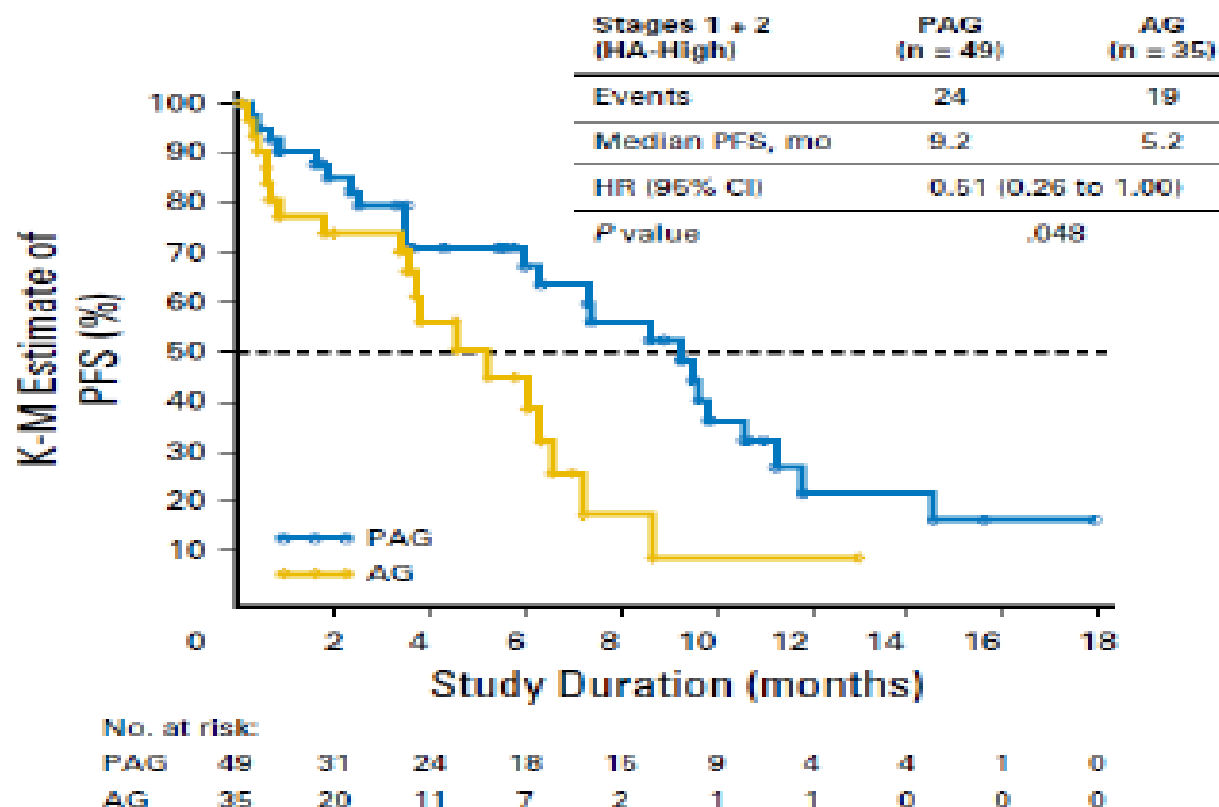
Provenzano et. al., Cancer Cell, 21, 2012

Phase II trial

PEGPH20 in Clinic (Phase II)

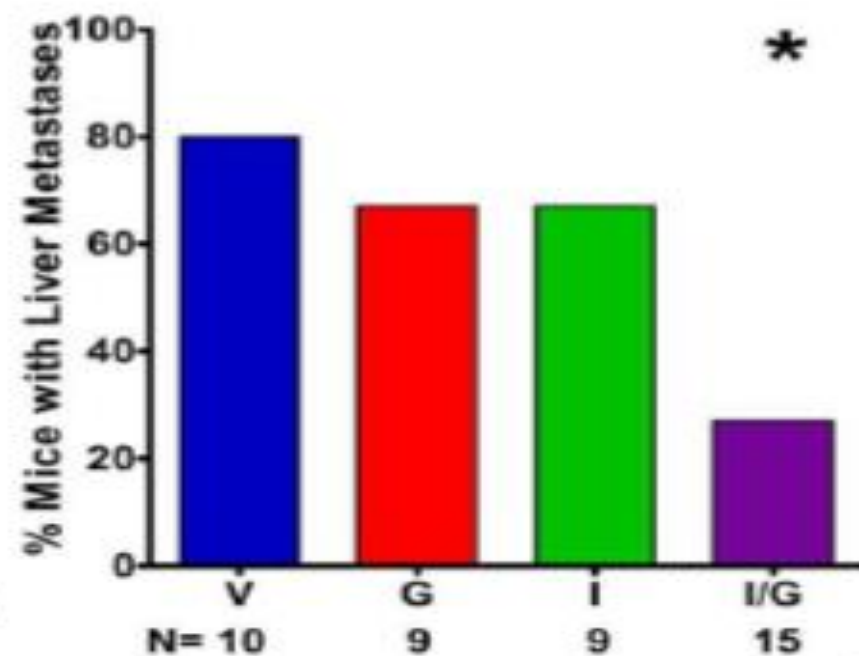
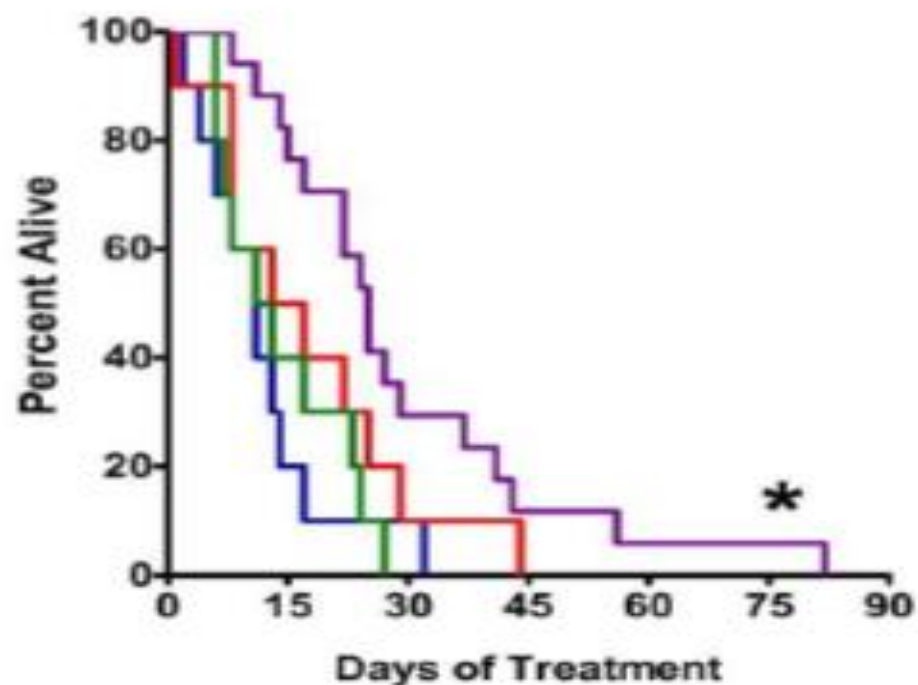
- Patients with advanced pancreatic cancer
- Arms:
 - Gem + nab-p
 - Gem + nab-p + PEGPH20
- No difference in PFS in the whole study population (negative)
- Pre-specified subgroup analysis:
 - Hyaluronin(HA) high patients

Phase 3 study was just reported negative in press release



Hedgehog signaling

Inhibition of Hedgehog Signaling Depleted Stroma, Enhanced Drug Delivery and Improved Survival in Mice

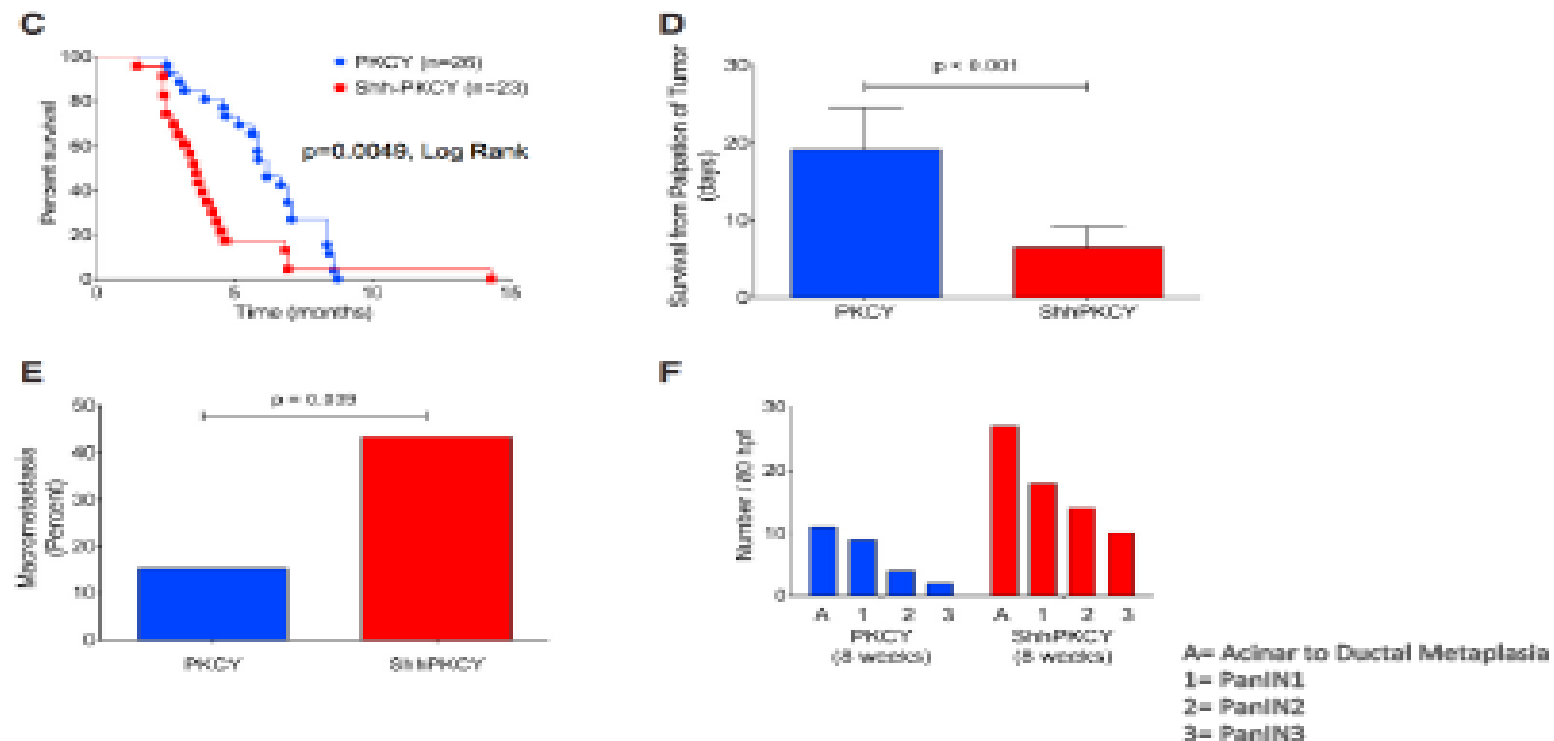


Olive KP et. al., Science, 324, 2009

Tumor suppressor

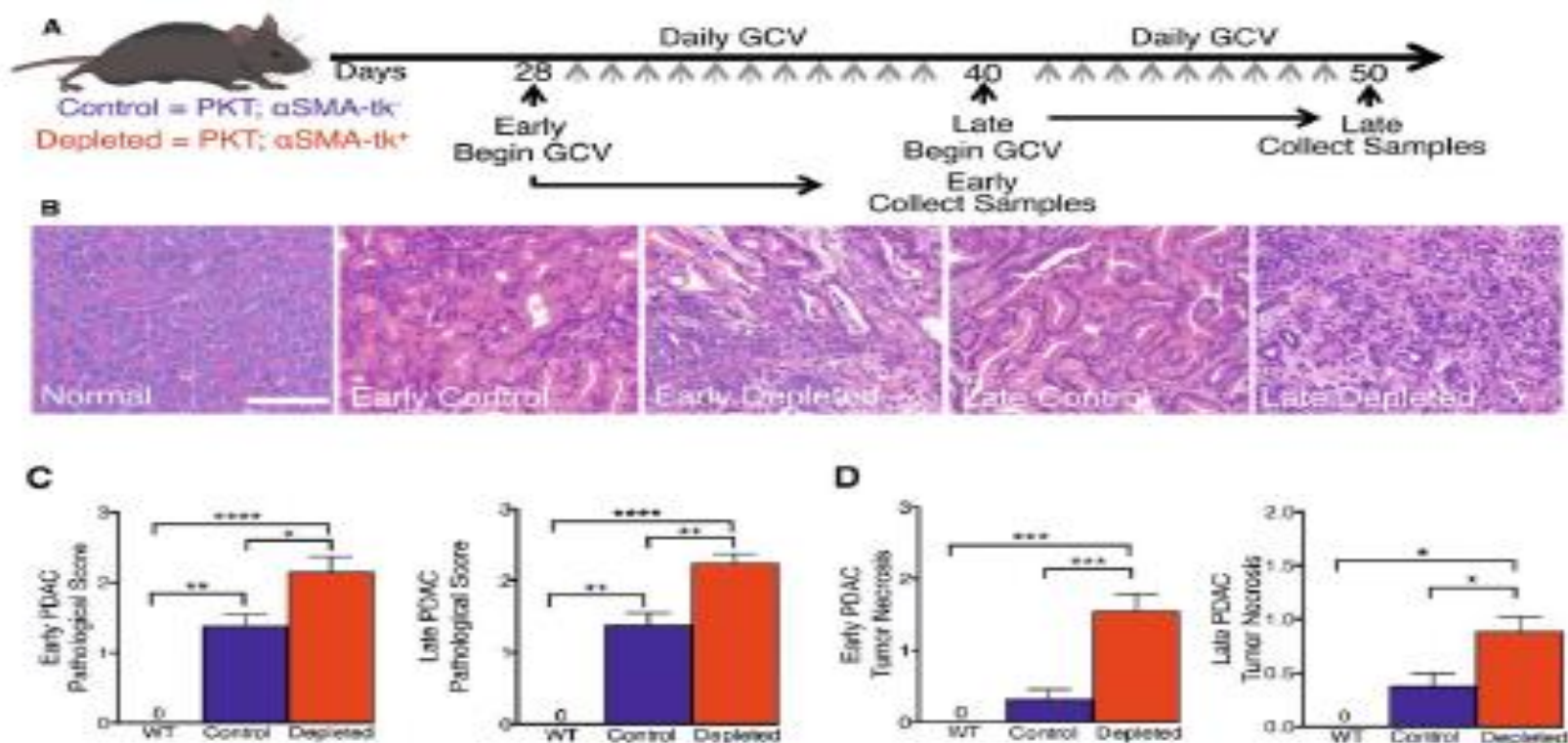
Sonic Hedgehog as a Tumor Suppressor in PDAC

Genetically Engineered Mouse Model



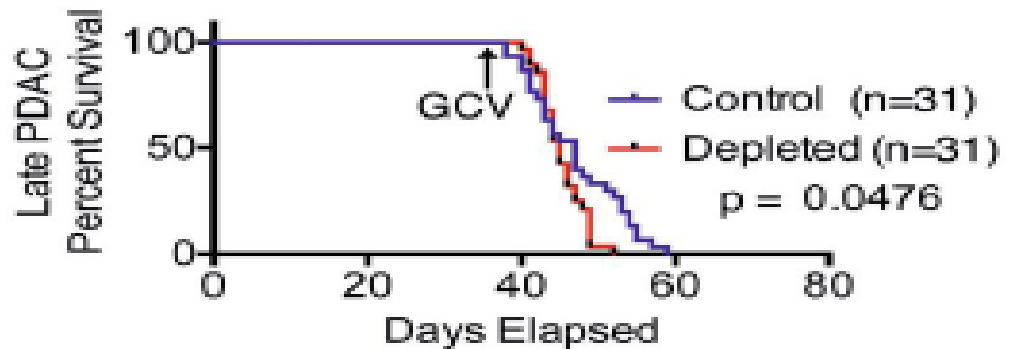
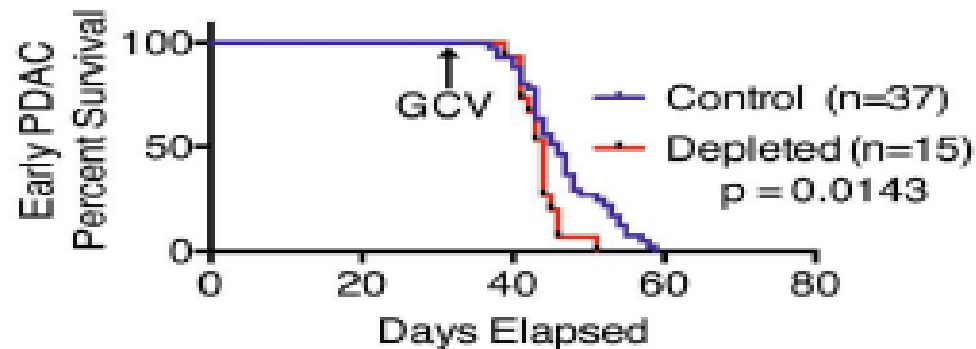
Myoblast depletion

Myofibroblast depletion enhances PDAC



Overall survival

Myofibroblast depletion reduces overall survival



GCV= genciclovir (Depletes Myofibroblasts in PKT; α SMA-tk+ Mice)

Anti-stromal therapy

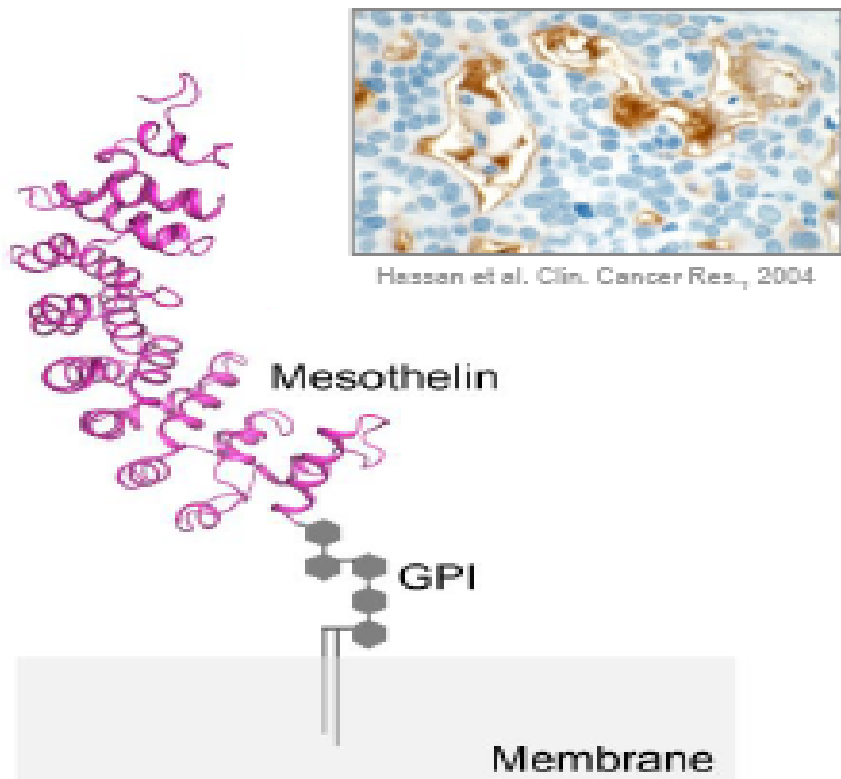
Two Faces of Anti-Stromal Therapy

**Stromal-targeting may not (always)
have beneficial therapeutic response**

Tumor-Stromal interaction is complex
and caution is required for therapeutic approaches
targeting stroma

Mesothelin

My Research: Mesothelin-Targeted Therapy for Pancreatic Cancer



Hassan et al. Clin. Cancer Res., 2004

CANCER

- Cancer-specific surface antigen expressed by many solid tumors
 - Mesothelioma
 - **Pancreatic**
 - Ovarian
 - NSCLC
 - Gastric
 - Endometrial*
 - Cervical*
 - Thymic carcinoma*
 - Cholangiocarcinoma*

NORMAL

- Normal expression limited to mesothelial cells
- No expression parenchyma of vital organs
- No phenotype in MSLN KO mice

Ma et al, J. Biol. Chem., 2012

MSLN expression

MSLN expression in pancreas ductal adenocarcinoma (PDA)

(C) Pancreatic ductal adenocarcinoma (5B2 antibody)

Negative	1+ (1-25% cells) ^s	2+ (26-50% cells)	3+ (>50% cells)	Total	Reference
0/60	10/60	50/60		60/60 (100%)	Argani <i>et al.</i> (5)*
0/14	3/14	5/14	6/14	14/14 (100%)	Frierson <i>et al.</i> (2)* ^s
1/11	0/11	2/11	8/11	10/11 (91%)	Ordonez (6)*
2/14	0/14	3/14	9/14	12/14 (86%)	Ordonez (1)*
7/68	22/68	39/68		61/68 (90%)	Swierczynski <i>et al.</i> (7)* [#]
0/18	2/18	1/18	15/18	18/18 (100%)	Hassan <i>et al.</i> (8)*
10/185 (5.4%)	37/185 (20%)	138/185 (75%)		175/185 (95%)	Total prevalence

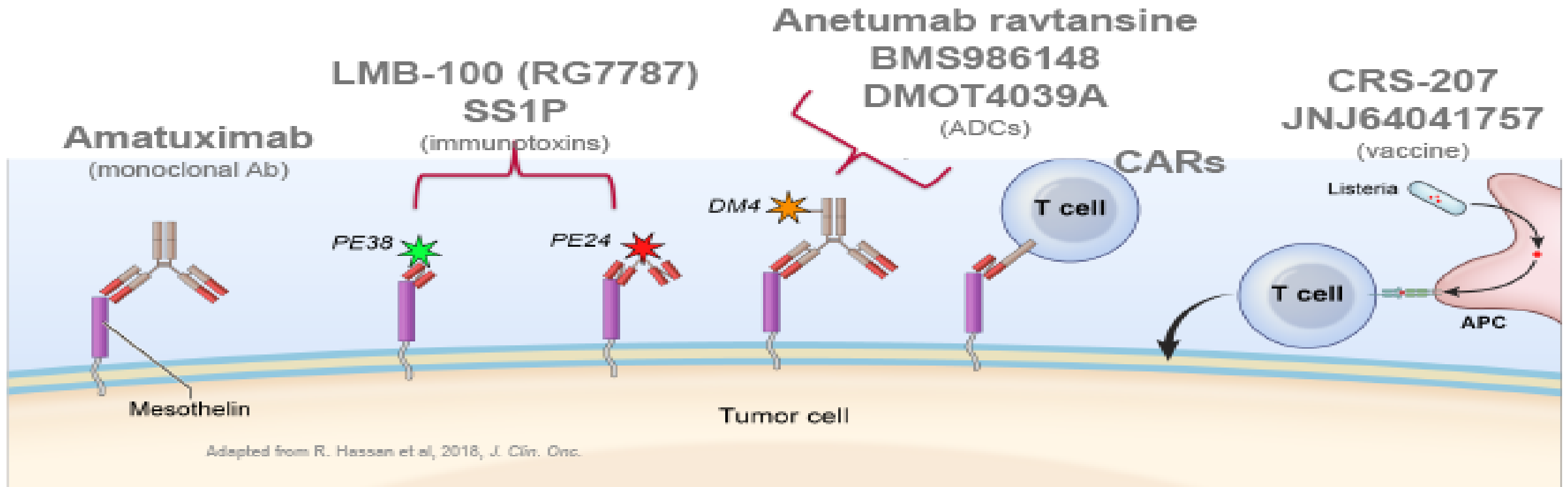
5%

20%

75%

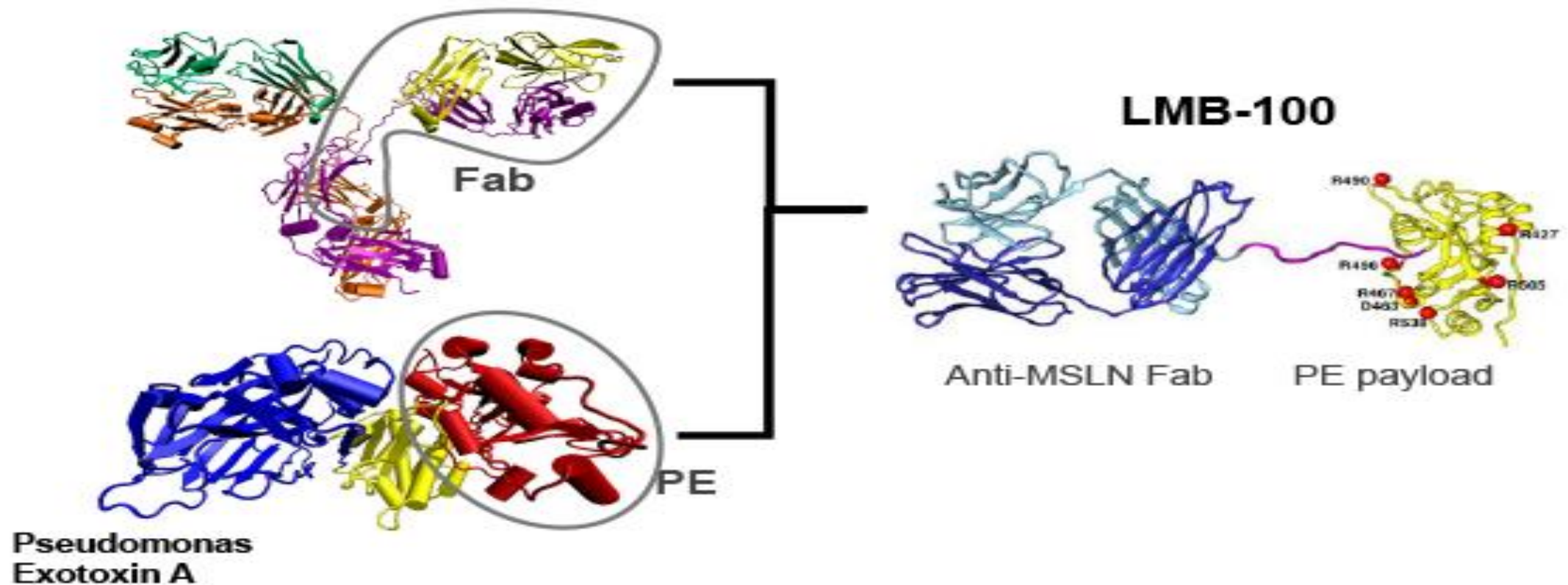
MSLN therapeutics

MSLN-targeted therapeutics in the clinic



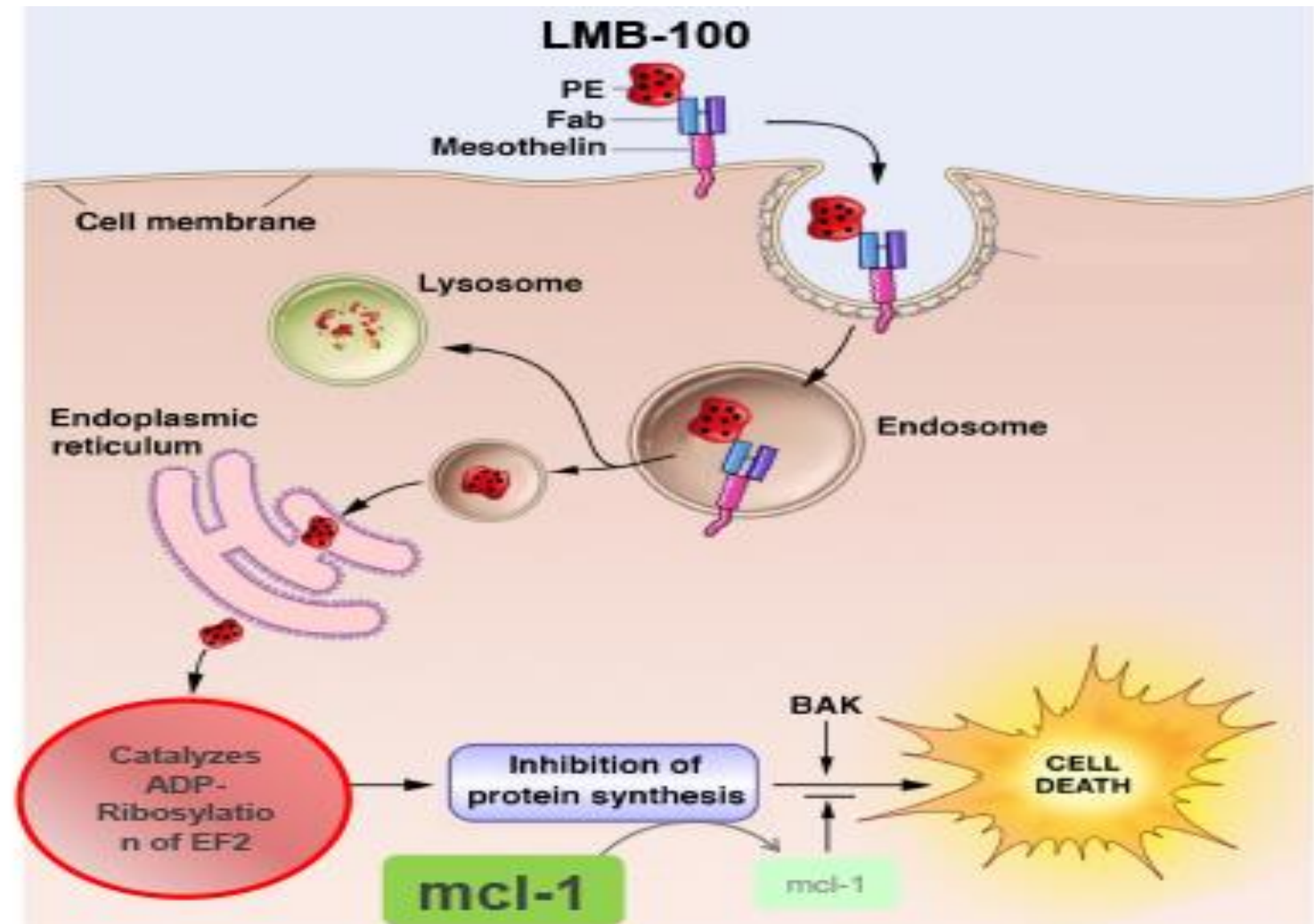
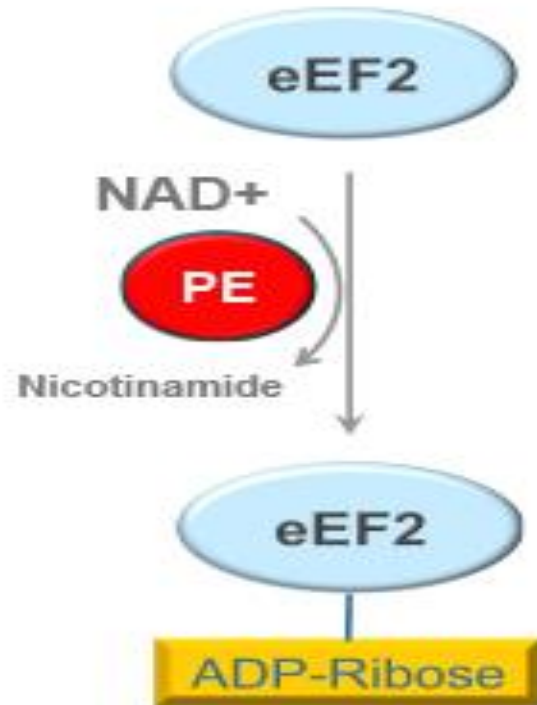
Recombinant immunotoxin

Recombinant Immunotoxin (iTox)



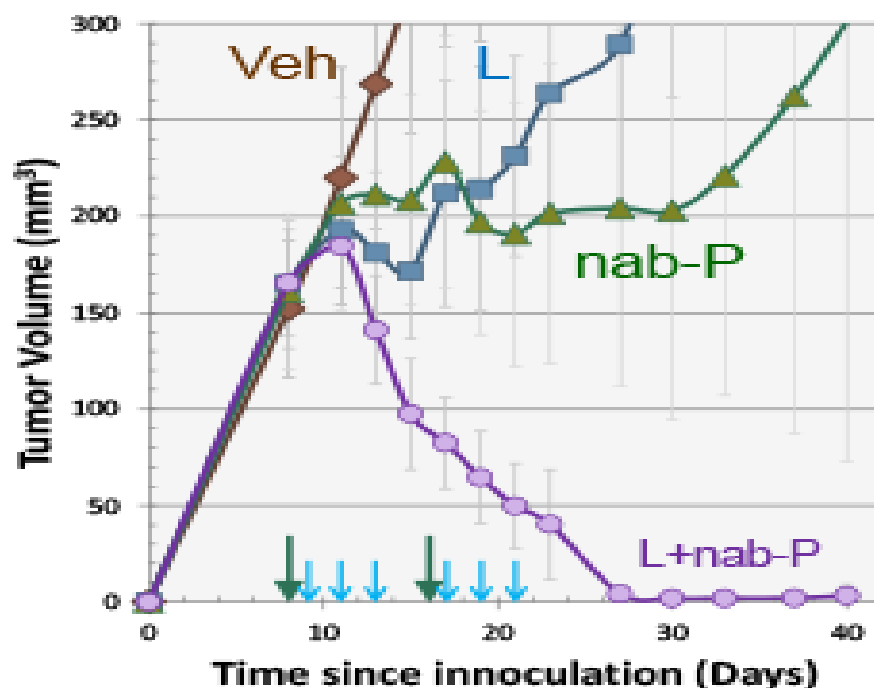
Mechanism of action

Mechanism of Action

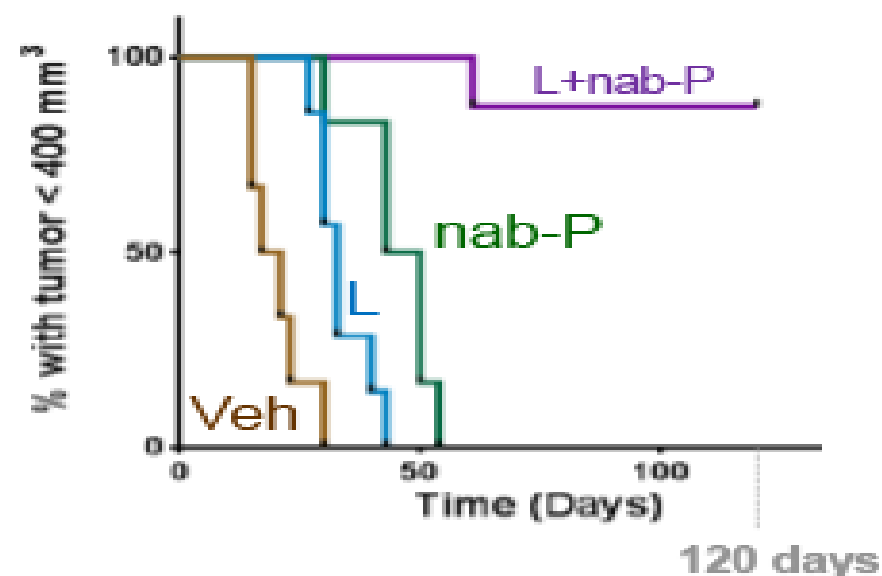


LMB-100 plus paclitaxel

LMB-100 works with nab-paclitaxel to eliminate PDAC tumors



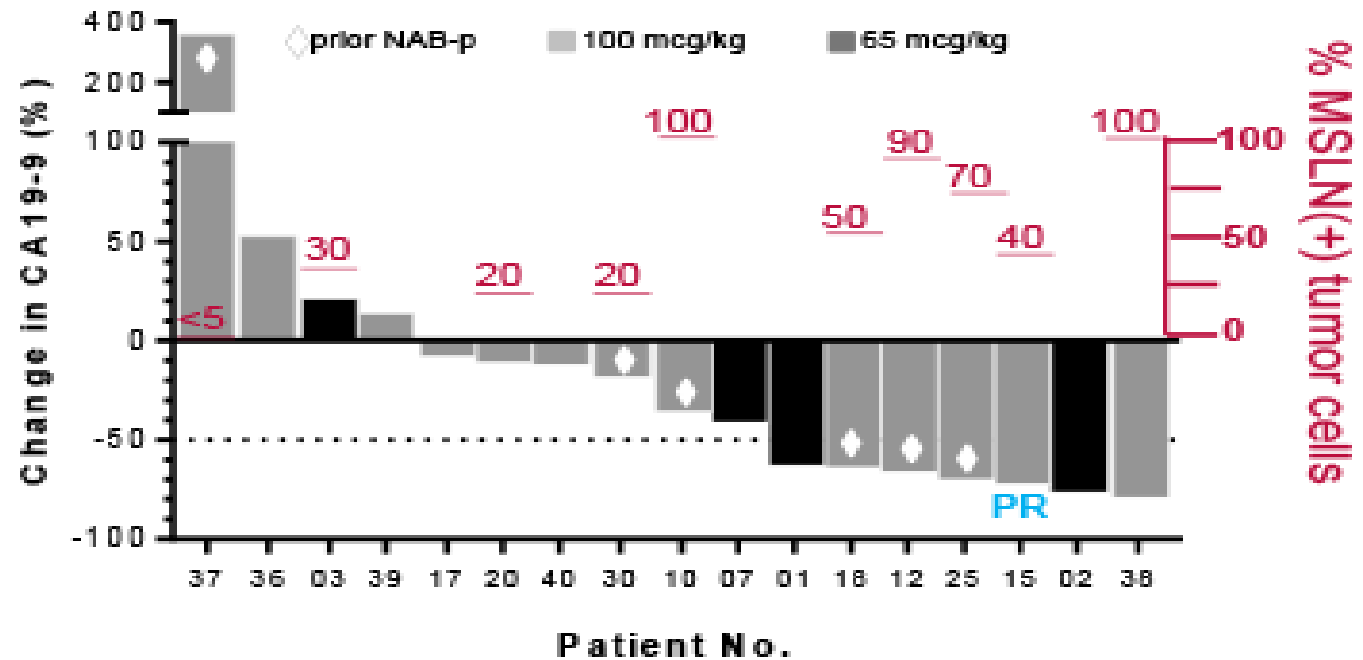
L = LMB-100 (2.5 mg/kg)



Active regimen

LMB-100 + NAB-paclitaxel is an active regimen

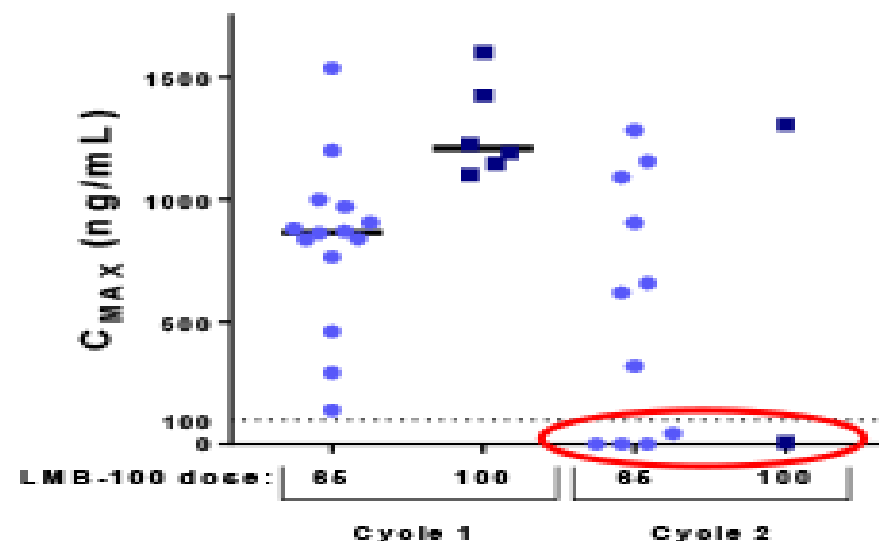
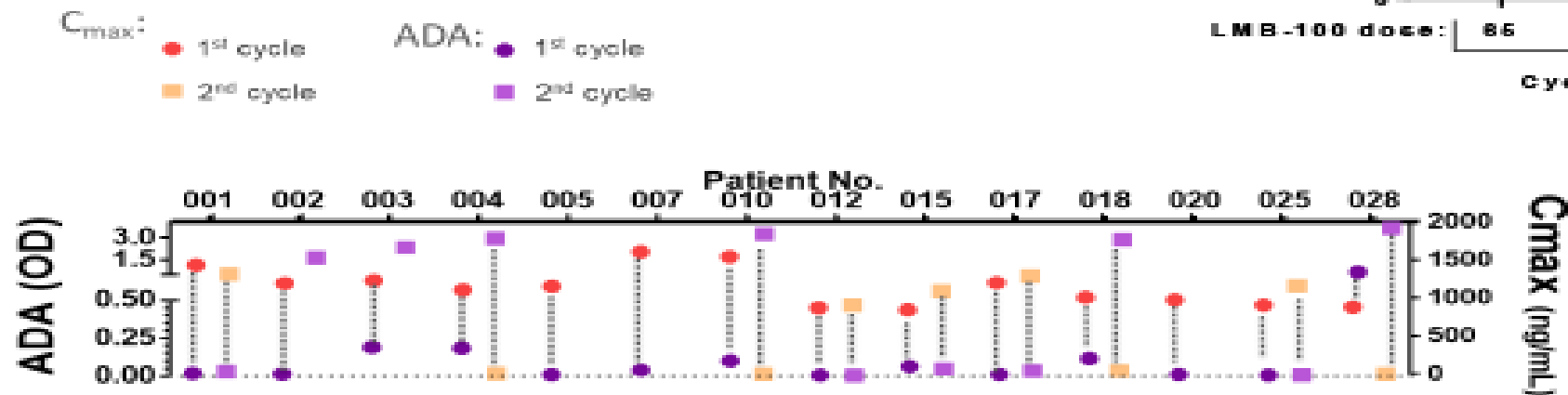
Better response is associated with higher MSLN expression in archival tissue



Anti-drug antibody

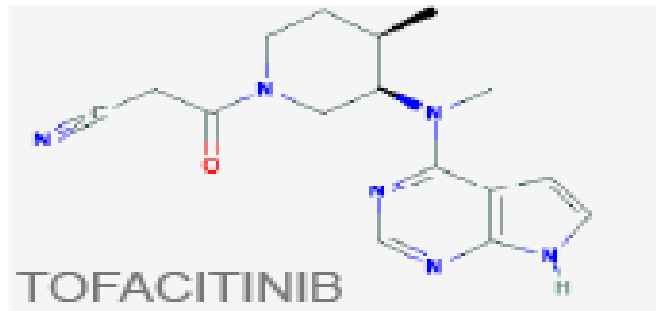
Alewine et al, *in press Clin. Canc. Res.*

Peak serum levels of LMB-100 are limited by anti-drug antibody formation beginning with Cycle 2

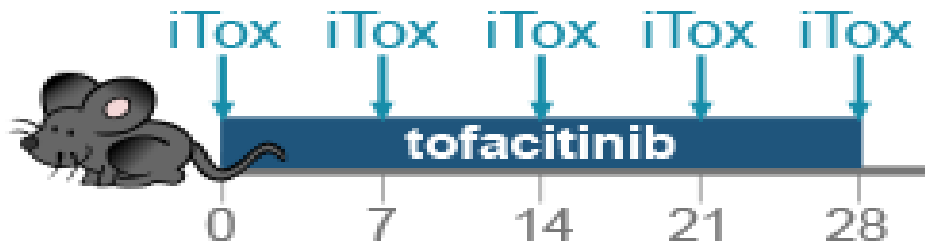


Decreasing ADA

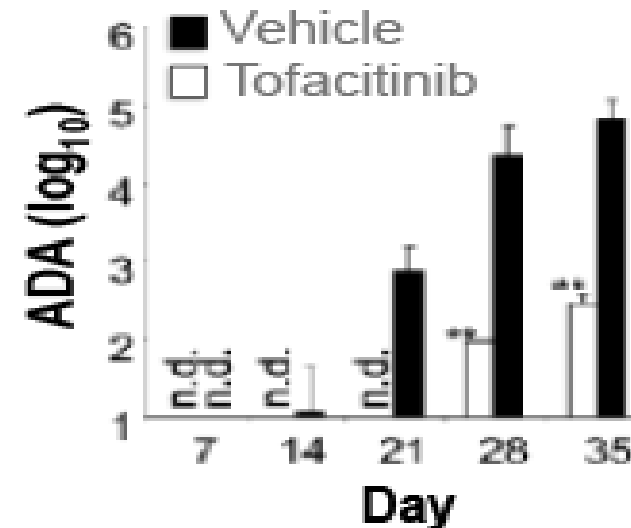
Decreasing ADA formation with tofacitinib



- Janus kinase (JAK) inhibitor
- Inhibits lymphocyte signaling
- FDA approved for treatment of autoimmune diseases
- Limits formation of ADAs against iTox in mice



Onda...Fitzgerald, *J. Immunol.*, 2014

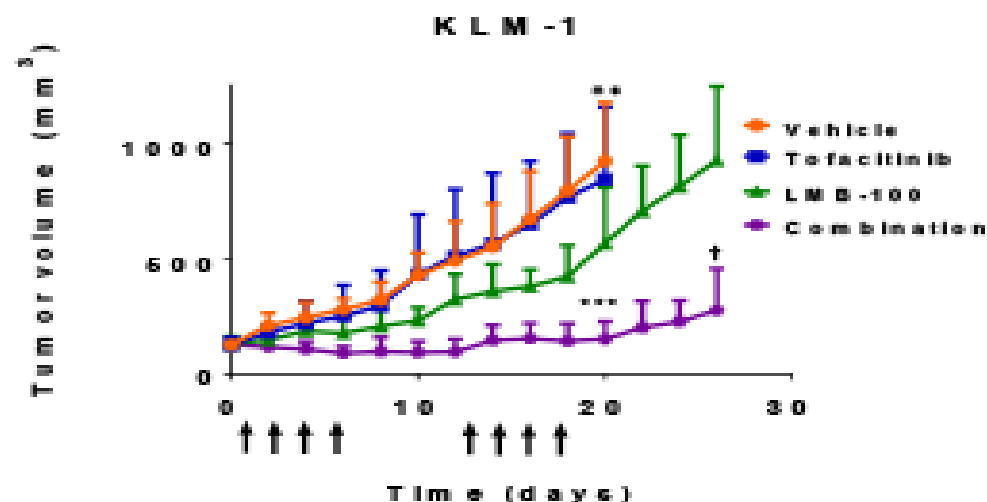


Tofacitinib

Additional effect of tofacitinib: increased anti-tumor efficacy through stromal modulation

Tofacitinib treatment

- Reduces macrophage population in tumors
 - Less non-specific uptake of iTox in tumor by macrophages
- => Increases iTox serum half-life
- => Increases iTox delivery to tumor



Tocacitinib + LMB-100

Phase I: tofacitinib + LMB-100

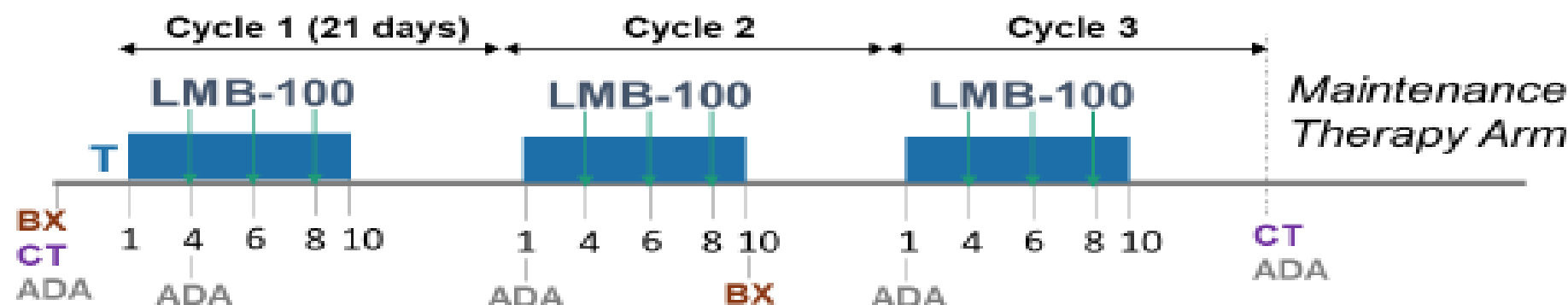
Now accruing!

1. Dose escalation to determine maximum tolerated dose

- MSLN(+) solid tumors

2. Expansion phase to assess impact on ADA formation

- Pancreatic adenocarcinoma
- extrahepatic cholangiocarcinoma



Tofacitinib (T)
LMB-100

10 mg PO, BID
as per dose escalation

CT = imaging
BX = optional tumor biopsy
ADA = anti-drug antibody titer

Questions?



Questions?